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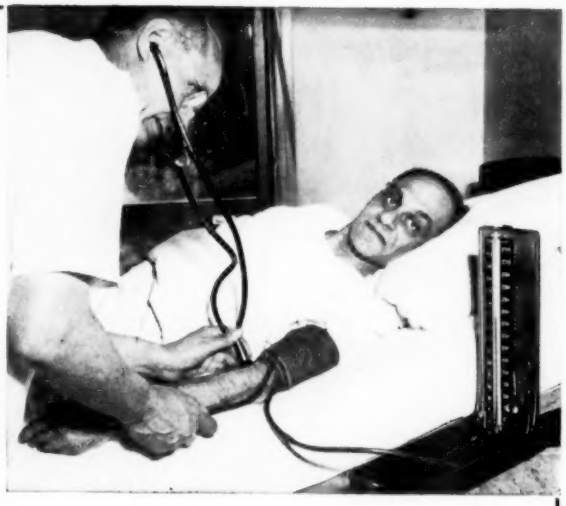

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1951

ORIGINAL ARTICLES

NPH INSULIN: ITS COMPARISON WITH PREVIOUS INSULIN REGIMENS

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AN ideal insulin has been defined as a preparation which upon deposit in tissues will release its hypoglycemic effect in response to metabolic demands. That is to say, the ideal insulin is one that mimics the function of the islets of Langerhans. None of the present-day insulins fulfills this definition, hence search for such an insulin has continued. Recently a new insulin, NPH (NPH 50), has been introduced[1,2,5,7,9,12,13]. Although NPH insulin again is not the ideal insulin, it does represent further progress. We are reporting our results with this insulin, especially in regard to its comparison with previous insulin regimens.

Methods. Forty-one patients were selected from cases hospitalized on the metabolic service of Dr. Edward S. Dillon. The patients were selected at random. Only those whose associated medical conditions might have affected insulin requirements were excluded. Weighed and calculated diets were given in a constant amount as prepared in the diet kitchen, a unit of the metabolic department. The amount of exercise by the patients can be considered constant during the period of study.

Insulin therapy prior to conversion to NPH insulin consisted of protamine-zinc, regular, or unmixed combinations. These preparations were used until standardization was achieved. Briefly, the criteria of standardization were: adequate diet, satisfactory fasting blood sugar, blood sugar during the entire 24-hour period between 80 and 180 mg. per 100 cc., no hypoglycemic reactions, urine sugar-free or less than 10 gm. per 24 hours, and no symptoms relative to diabetes mellitus. Numerous blood glucose determinations and quantitative urine sugar tests were performed during standardization. The final values charted for the blood glucose were obtained during a single 24-hour period. NPH insulin† in approximately the same amount was then given for not less than 4 days and the same criteria of standardization were used. The 2 insulin programs were separated by a relatively short period of time.

* Resident in Medicine.
† Generously supplied by Eli Lilly and Co., Indianapolis.

TABLE 1.—COMPARISON OF INSULIN DOSAGE AND BLOOD GLUCOSE VALUES PRIOR TO AND ON NPH INSULIN

Patient No.	Age	Dur. Diab. yr.	Insulin dose				Blood glucose values (mg. per 100 cc.)			
			B	L	S	N	F	2 hr.	3 p.m.	9 p.m.
1	63	0.3	10 PZI	0	0	0	109	125	115	109
			10 NPH	0	0	0	115	123	114	111
2	63	5	10 PZI	0	0	0	115	195	—	150
			10 NPH	0	0	0	95	155	155	120
3	63	5	10 PZI	0	0	0	88	142	—	150
			10 NPH	0	0	0	95	146	123	115
4	60	0.2	12 PZI	0	0	0	100	167	—	173
			10 NPH	0	0	0	95	134	—	177
5	62	6	10 PZI	0	0	0	92	173	—	203
			10 NPH	0	0	0	103	102	—	125
6	56	15	15 PZI	0	0	0	105	188	—	155
			15 NPH	0	0	0	100	146	129	115
7	50	0.2	18 PZI	0	0	0	61	216	—	155
			18 NPH	0	0	0	109	173	150	146
8	68	10	20 PZI	0	0	0	105	168	—	155
			20 NPH	0	0	0	111	138	—	115
9	41	N	20 PZI	0	0	0	123	100	—	134
			20 NPH	0	0	0	118	95	92	95
10	64	5	22 PZI	0	0	0	98	173	—	177
			22 NPH	0	0	0	150	125	173	177
11	80	N	25 PZI	0	0	0	58	150	—	276
			22 NPH	0	0	0	100	159	—	155
12	61	13	28 PZI	0	0	0	88	75	—	192
			28 NPH	0	0	0	98	159	—	150
13	68	17	38 PZI	0	0	0	88	184	—	167
			35 NPH	0	0	0	138	134	—	174
14	53	20	45 PZI	0	0	0	111	183	—	303
			45 NPH	0	0	0	83	146	207	163
15	60	N	15 R	10R	10R	5R	105	177	—	142
			32 NPH	0	0	0	111	138	—	199
16	48	N	15 R	15R	10R	5R	118	125	—	134
			35 NPH	0	0	0	125	155	—	146
17	42	N	15 R	10R	15R	0	173	192	—	155
			36 NPH	0	0	0	150	173	174	142
18	40	N	25 R	15R	15R	0	105	150	135	120
			45 NPH	0	0	0	100	109	83	98
19	40	N	20 R	15R	20R	15R	88	192	150	142
			60 NPH	0	0	0	109	199	120	118
20	60	20	10 PZI & 10 R	0	0	0	115	150	—	175
			20 NPH	0	0	0	110	205	160	205
21	50	0.5	15 PZI & 10 R	0	0	0	129	199	—	184
			25 NPH	0	0	0	109	138	—	159
22	56	N	16 PZI & 10 R	0	0	0	135	210	—	150
			25 NPH	0	0	0	155	225	220	180
23	63	2	12 PZI & 15 R	0	0	0	100	160	180	130
			28 NPH	0	0	0	130	175	95	150
24	61	13	20 PZI & 10 R	0	0	0	107	134	—	193
			30 NPH	0	0	0	109	138	—	83
25	33	10	30 PZI & 10 R	0	0	0	88	160	—	155
			36 NPH	0	0	0	100	150	—	144
26	68	18	30 PZI & 15 R	0	0	0	98	138	—	249
			40 NPH	0	0	0	100	209	—	163

TABLE 1. COMPARISON OF INSULIN DOSAGE AND BLOOD GLUCOSE VALUES PRIOR TO AND ON NPH INSULIN (*Continued*)

Patient No.	Age	Dur. Diab. yr.	Insulin dose				Blood glucose values (mg. per 100 cc.)			
			B	*L*	*S*	*N*	*F*	*2 hr.*	*3 p.m.*	*9 p.m.*
27	27	N	16 PZI & 15 R	0	0	0	120	175	—	160
			40 NPH	0	0	0	65	155	195	175
28	47	10	25 PZI & 20 R	0	0	0	88	111	—	146
			40 NPH	0	0	0	100	130	—	112
29	70	N	30 PZI & 15 R	0	0	0	165	155	—	80
			45 NPH	0	0	0	135	150	180	110
30	29	6	34 PZI & 16 R	0	0	0	75	75	—	124
			46 NPH	0	0	0	83	188	177	61
31	76	3	40 PZI & 10 R	0	0	0	122	130	—	150
			48 NPH	0	0	0	115	135	—	118
32	45	N	32 PZI & 20 R	0	0	0	129	150	—	188
			50 NPH	0	0	0	100	134	—	188
33	66	13	18 PZI & 35 R	0	0	0	111	95	—	163
			50 NPH	0	0	0	95	222	—	192
34	72	40	40 PZI & 15 R	0	0	0	75	125	—	100
			50 NPH	0	0	0	112	65	—	180
35	74	22	40 PZI & 15 R	0	0	00	138	64	—	209
			50 NPH	0	0	0	78	222	—	173
36	50	7	34 PZI & 20 R	0	0	0	98	134	—	276
			52 NPH	0	0	0	69	134	192	184
37	17	0.5	40 PZI & 15 R	0	0	0	61	115	—	167
			52 NPH	0	0	0	73	109	167	118
38	65	16	20 PZI & 35 R	0	0	0	129	203	—	204
			55 NPH	0	0	0	95	209	—	184
39	52	4	44 PZI & 20 R	0	0	0	85	188	—	210
			60 NPH	0	0	0	89	123	—	177
40	38	0.3	75 PZI & 20 R	0	0	0	73	73	—	163
			100 NPH	0	0	0	159	155	163	173
41	56	10	40 PZI & 80 R	0	0	0	80	220	160	60
			100 NPH	0	0	0	75	225	180	145

Key: *B*—breakfast; *L*—lunch; *S*—supper; *N*—night; N—new diabetic; F—fasting specimen; R—Regular insulin (quick-acting); PZI—Protamine-zinc insulin

Blood glucose values were determined by Nelson's modification of the Somogyi method using oxalated venous blood[8]. Some of the 9 p.m. specimens were placed in special fluoride tubes, refrigerated, and the blood glucose levels determined 12 hours later; these levels have been found to be constant for as long as 72 hours. Urine glucose content was also determined by Nelson's method. All chemical determinations were performed by technicians in the metabolic laboratory.

Results. A comparison of insulin dosage and blood glucose values on the 2

insulin regimens is listed in Table 1. All patients were males. Their ages ranged from 17 to 80 years with all but 4 above the age of 40. Diabetes was recently discovered in 11 cases; the duration of the diabetes in the remaining cases ranged from 2 months to 40 years. Fourteen patients were standardized on protamine-zinc insulin, five were standardized on regular insulin, and 22 were standardized on unmixed combinations of protamine-zinc and regular insulin. With the exception of the 5 patients who received only regular insulin, the daily insulin requirement was administered before breakfast. The patients on regular insulin alone were given insulin prior to each meal and, when indicated, an additional dose at 2 a.m. All were transferred to a single dose of NPH insulin before breakfast. Blood glucose values on the 2 insulin regimens are listed.

Discussion. NPH insulin was perfected by Krayenbühl and Rosenberg in Hagedorn's laboratory[6]. It is a highly purified suspension of insulin, protamine, and zinc crystals. It differs basically from protamine-zinc insulin in its protamine content. Protamine-zinc insulin contains approximately 1.25 mg. of protamine per 100 units of insulin, whereas NPH insulin contains approximately 0.5 mg. of protamine per 100 units of insulin. NPH insulin, an isophane, contains just enough protamine to combine with the insulin. Therefore, should this preparation be mixed with regular insulin, there would be no excess protamine available for the formation of more long-acting insulin. It becomes obvious from this that NPH insulin is the ideal long-acting insulin with which mixtures should be made. From the available work on NPH insulin[3,4,9-11] the time action curve of this new preparation has been established. This insulin usually acts promptly enough to control the post-prandial rise in blood sugar; it reaches its peak effect in approximately 8 hours; and its duration of action is approximately 24 hours. This time action curve is very similar to that of a 2:1 mixture of regular and protamine zinc insulins.

It is difficult to evaluate the severity of diabetes in a given patient on the basis of insulin dosage alone. The patients in this study included mild, moderate, and moderately severe cases of diabetes mellitus. The labile or brittle diabetic was not included. Nineteen of the 41 cases required 40 or more units of NPH insulin per day.

The time action curve of NPH insulin in this series of cases was evaluated by a consideration of the blood glucose levels at 4 periods throughout the day. Using the fasting blood glucose level as a judge of long-action effect of insulin, it was found that NPH insulin was as good in this respect as the previous regimens in all cases except 2 (Cases 10, 40). An explanation for these 2 cases, which show a lesser predominence of nocturnal insulin action on NPH, may be found if one considers the fasting blood sugar in relation to the 9 p.m. blood sugar.

The post-prandial effect of NPH insulin is due to its rapid onset of action, and perhaps to a lesser degree to some overlap from the previous day's dose. When compared with those patients who had formerly received only protamine-zinc insulin, the post-prandial effect of NPH insulin was superior in all instances. In comparison with cases receiving protamine-zinc insulin and regular insulin, the post-prandial blood glucose levels were at least as good, except in Cases 20, 26, 33, 35, and 41. Two of these 5 cases (No. 33, 41) received large amounts of regular insulin in proportion to the total dose, which may account for the lower 2-hour blood glucose levels obtained on the first regimen. Case 41, obviously a "post-prandial riser," may be con-

sidered evidence for a strong quick-acting component of NPH insulin. This patient on the former dose of 40 units of protamine-zinc insulin plus 80 units of regular insulin had a difference of 140 mg. per 100 cc. between the fasting and the 2-hour blood glucose level. On a dose of only 100 units of NPH insulin there was a rise of 180 mg. per 100 cc. in this same period, which is a comparable rise.

We observed no clinical evidence of hypoglycemic reaction in this group of patients. The blood glucose levels fallen between 80 and 180 mg. per 100 cc., with the notable exception of the post-prandial period.

General rules for the transfer of other patients to NPH insulin are: Patients requiring less than 40 units of protamine-zinc insulin or protamine-zinc insulin and regular insulin per day can be safely converted to the same total dose of NPH insulin; for patients requiring more than 40 units of insulin per day, the NPH insulin dose is equal to the total protamine-zinc in-

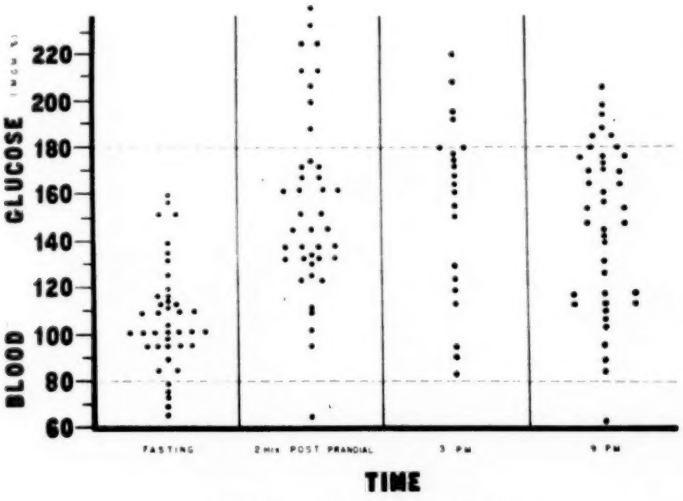

FIG. 1.—Blood glucose levels with NPH insulin.

taken on 21 cases at 3 p.m., the expected time of peak NPH action, were satisfactory.

The last period of study was at 9 p.m. These values, taken while the patients were on NPH, were in almost all cases better than the values for blood glucose taken while the patients were on the former regimens.

A composite of the blood glucose levels on NPH insulin during the 4 described periods is recorded in Fig. 1. Most of the values may be seen to have

sulin dose plus 80% of the regular insulin dose.*

Summary. 1. The blood glucose levels with NPH insulin and with previous insulin regimens were compared in 41 hospitalized patients.

2. The dietary intake, exercise, and associated medical conditions were kept constant during the period of study.

3. The post-prandial effect of NPH insulin was superior in all cases which had previously received only prota-

* Subsequent experience with a large number of cases has upheld these rules.

mine-zinc insulin. In almost all cases previously on combinations of protamine-zinc and regular insulins, the post-prandial blood glucose levels were as good on NPH insulin. This is further evidence for a quick onset of action of NPH insulin.

4. The fasting, 3 p.m. and 9 p.m. blood glucose levels were generally more satisfactory on NPH insulin than on the previous regimens.

5. General rules for the transfer of other patients to NPH insulin are given.

6. NPH insulin is a valuable addition to the insulin armamentarium because it best meets the need of a large proportion of patients with diabetes mellitus.

REFERENCES

1. **Dolger, H.**: Proc. Am. Diabetes Assn., **9**, 213, 1949.
2. **Gabriele, A. J.**, and **Marble, A.**: Am. J. Digest. Dis., **16**, 197, 1949.
3. **Izzo, J. L.**: Proc. Am. Diabetes Assn., **9**, 225, 1949.
4. Idem, and **Crump, S. L.**: J. Clin. Investigation, **29**, 1514, 1950.
5. **Kirkpatrick, N. R.**: Proc. Staff Meet., Mayo Clin., **24**, 365, 1949.
6. **Krayenbühl, C. H.**, and **Rosenberg, G.**: Reports of Steno Mem. Hosp., **1**, 60, 1946.
7. **Marble, A.**, and **Gabriele, A. J.**: Proc. Am. Diabetes Assn., **9**, 215, 1949.
8. **Nelson, N.**: J. Biol. Chem., **153**, 375, 1944.
9. **Peck, F. B.**: Proc. Am. Diabetes Assn., **6**, 273, 1946.
10. Idem: M. Clin. No. Amer., **31**, 343, 1947.
11. **Rohr, J. H.**, and **Colwell, A. R.**: Proc. Am. Diabetes Assn., **8**, 3, 1948.
12. **Sprague, R. G.**: Ann. Int. Med., **31**, 628, 1949.
13. **White, P.**: J. Am. Med. Assn., **141**, 312, 1949.

THE INTERRELATIONSHIP OF VITAMIN K AND DICOUMARIN*

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AND

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ALTHOUGH the early work on spoiled sweet clover hay suggested that foods rich in vitamin K, such as alfalfa, afforded some protection against the toxic principle,[11,16,17] it was not until dicoumarin was isolated and natural vitamin K_1 and compounds having strong vitamin K activity became available, that the problem could be studied successfully. In 1942 Overman, Stahmann, and Link[10] showed that both natural and synthetic vitamin K's in relatively large doses had an antagonistic effect on the action of dicoumarin. Lehmann[7] and later Shapiro, Redish, and Campbell[18] observed that hypoprothrombinemia induced by dicoumarin in man likewise responded to vitamin K. Cromer and Barker[2] showed that large doses of 2-methyl-1,4-naphthoquinone bisulfate (Hykinone) successfully counteracted dicoumarin. Recently Boyd and Warner[1] failed to note any action of either menadione or menadione bisulfite on the hypoprothrombinemia induced by dicoumarin in rats. Davidson and MacDonald[3] observed that while synthetic vitamin K compounds were ineffective in counteracting the action of dicoumarin, large doses of vitamin K_1 oxide prevented or reversed the hypoprothrombinemia of this drug. Recently several groups of investigators[5,8,20] have confirmed that natural vitamin K_1 is the more efficient.

In the present investigation conditions were devised which permitted a more concise and quantitative study of the relationships of the actions of vitamin K and dicoumarin. By employing dogs that had a cholecystnephrostomy, it was possible to eliminate the effect of stored vitamin K, since the lack of bile salts in the intestines prevented the animal from absorbing vitamin K and compelled the organism to exhaust its reserve supply, as shown by Hawkins and Brinkhous[4] and by Smith and his associates.[21]

Methods. The prothrombin was determined by the 1-stage method. The normal prothrombin time for dog plasma was 6 seconds. Cholecystnephrostomy was performed by the operation devised by Kapsinow, Engle, and Harvey[6].

Dicoumarin solution: 250 mg. of dicoumarin were dissolved in 16 cc. of hot 0.1-N NaOH and diluted to 50 cc. The dicoumarin was always administered intravenously. A standard dose of 1 mg. per kg. of body weight was selected since this is approximately the minimum amount which will affect the prothrombin level in normal dogs[12] and if given daily will be slightly cumulative. The standard dose of vitamin K_1 selected was 10 γ per kg. of body weight.

Three synthetic compounds: 2-methyl-1,4-naphthoquinone (menadione); 2-methyl-1,4-naphthohydroquinone 3-sodium sulfonate (Hykinone, Abbott) and 2-methyl-1,4-naph-

* This work was supported by a grant from the Division of Research Grants, National Institutes of Health.

† The data presented are part of a thesis presented to the Graduate School of Medicine, University of Pennsylvania for the degree of Master of Science in Medicine.

thohydroquinone diphosphoric ester tetrasodium salt (Synkavite, Hoffmann-LaRoche) were tested and compared with vitamin K_1 on the basis of their molecular weights.

Results. Effect of Store of Vitamin K on Resistance to the Action of Dicoumarin. A normal well-fed dog was subjected to cholecystnephrostomy. The animal became increasingly more susceptible to the drug and after 3 months, the small standard dose of 1 mg. caused the prothrombin time to rise to 95 seconds in 72 hours. On injecting 10 γ of vitamin K_1 per kg. of body weight, the prothrombin level promptly returned to normal. This indicates that the marked susceptibility of the animal to dicoumarin was not due to hepatic dysfunction, but was primarily, if not solely, the result of a lack of stored vitamin K.

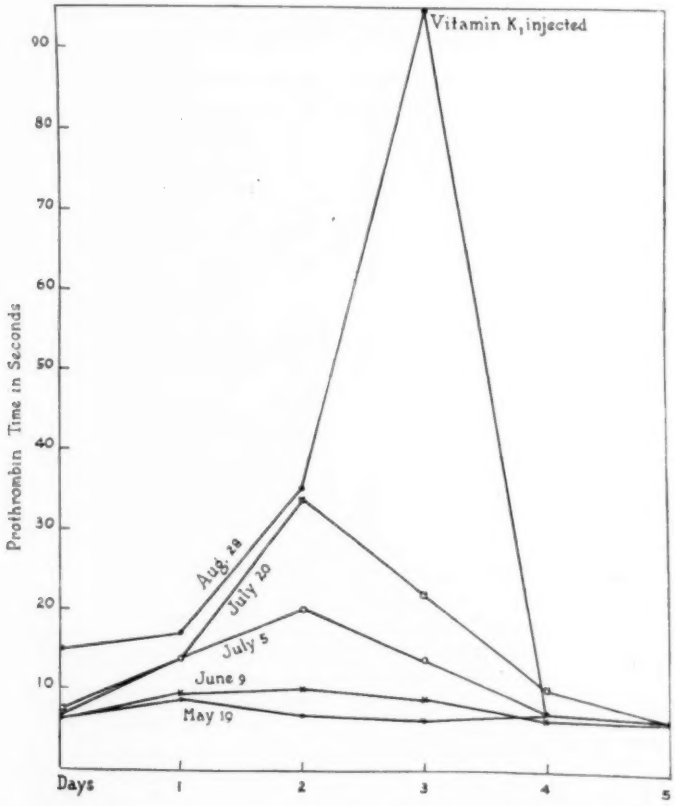


Fig. 1.—The increased susceptibility of the animal to dicoumarin as the store of vitamin K becomes depleted. A cholecystnephrostomy was performed on the dog May 12. The response of the animal to a single dose of 1 mg. of Dicoumarin per kg. of body weight was determined after varying intervals of time.

One week after the operation, he was given 1 mg. of dicoumarin per kg. of body weight. As seen in Fig. 1, the response was similar to that observed in a normal dog. Three weeks later, the effect from the same dose of dicoumarin was slightly more pronounced.

It was found that even as small a dose as 0.1 mg. of dicoumarin per kg. of

body weight could significantly elevate the prothrombin time in a cholecystnephrostomized dog. Thus in one instance, the prothrombin time increased from 11½ seconds to 19 seconds in 24 hours. Such a dose is entirely ineffective in a normal animal. These results emphasize the importance of employing for assay of dicoumarin and allied drugs only animals which have been on a standard diet for a long period. It has been observed that when as many as 24 rabbits which have been kept on a standard ration for several months are given a fixed dose of dicoumarin, the decrease in prothrombin is remarkably uniform. It would appear, therefore, that innate refractoriness may not be particularly common. There is, however, a definite species difference in response to dicoumarin. The chicken, for instance, is very resistant to the drug even when its vitamin K store is depleted[12,14].

TABLE 1.—THE EFFECT ON THE PROTHROMBIN LEVEL PRODUCED BY ADMINISTERING VITAMIN K AND DICOUMARIN SIMULTANEOUSLY

*Dose of drug per Kg. of body weight**	*Dog*	*Hours* 0	¼	2¼	5⅛	7.2	96
		Prothrombin time in seconds					
Vitamin K_1 10 γ	C	11	6	6			
	M	8	6	6			
Dicoumarin 1 mg.	B	8½	9	22	30	50	20
	M	6	6½	14	24½	24½	13
Dicoumarin 1 mg.	B	11	13	10	13	23	21
Vitamin K_1 10 γ	M	8	8	10	10	13	11½
Dicoumarin 1 mg.	C	11	11	10	15	13	
Menadione 10 γ	M	7	7	9½	8½	7½	
Dicoumarin 1 mg.	C	11	11	—	—	—	—
Hykinone 6.1 γ	H	7	7	7	7½	7	
Dicoumarin 1 mg.	C	11	11½	10	8	13½	13½
Synkavite 9.4 γ	M	7½	7½	7½	7½	7½	7½

* The molecular weights of vitamin K_1, menadione, Hykinone, and Synkavite are 450, 172, 275, and 422, respectively.

THE EFFECT OF ADMINISTERING DICOUMARIN AND VITAMIN K SIMULTANEOUSLY. Since the dog is exceedingly sensitive after cholecystnephrostomy to small doses of dicoumarin and his prothrombin level responds promptly to vitamin K, such an animal is particularly suitable for studying the direct antagonistic effect of vitamin K_1 and various synthetic vitamin K compounds to dicoumarin because the complicating influence of stored vitamin K is absent.

In Table 1 the results illustrate what happened when dicoumarin and vitamin K were injected simultaneously. It will be noted that the prothrombin concentration was little changed in 4 hours. Had no dicoumarin been given, the prothrombin would have returned to normal in 4 hours, as shown by the control which received only vitamin K_1. This suggests that dicoumarin promptly inhibits the action of vitamin K. This immediate inhibiting action of dicoumarin has not been clearly demonstrated previously, since the fall in prothrombin during the first few hours is too gradual to be measured accurately.

The counteracting influence of vitamin K on dicoumarin is also shown. The prothrombin concentration fails to fall significantly. Menadione, Hykinone, and Synkavite are essentially as active as vitamin K_1 in preventing the

action of dicoumarin. The fact that dicoumarin prevents vitamin K from correcting hypoprothrombinemia on the one hand, and that vitamin K, whether natural or synthetic, does not allow any significant drop in the prothrombin level after the injection of dicoumarin is strong evidence that vitamin K and dicoumarin act on the same agent or system.

THE EFFECT OF VITAMIN K ON THE HYPOPROTHROMBINEMIA INDUCED BY DICOUMARIN. To study how effectively vitamin K_1 and the synthetic vitamin K compounds can correct the hypoprothrombinemia induced by dicoumarin, the standard dose of 1 mg. of the drug per kilo of body weight was given intravenously to cholecystnephrostomized dogs, and after 2 days when the prothrombin time had dropped to a low level, 10 γ of vitamin K_1 or 1 of the 3 synthetic compounds was administered. From the results as recorded in Table 2 one can conclude that vitamin K_1 as well as menadione, Hykinone, and Synkavite can correct the hypoprothrombinemia induced by dicoumarin fairly promptly and effectively. The natural vitamin K_1 is the most effective and menadione the least.

It should be noted that when dicoumarin and vitamin K are administered simultaneously their actions are deadlocked. It may be postulated that 2 days after giving a minimum effective dose of dicoumarin, all of the drug is eliminated except the small fraction which is attached to the mechanism which synthesizes prothrombin. Similarly, when a dose of vitamin K is given just sufficient to restore the synthesis of prothrombin but not big enough to permit storage, the animal retains its susceptibility to dicoumarin.

TABLE 2.—THE EFFECTIVENESS OF NATURAL VITAMIN K AND SYNTHETIC VITAMIN K'S TO CORRECT THE HYPOPROTHROMBINEMIA CAUSED BY DICOUMARIN*

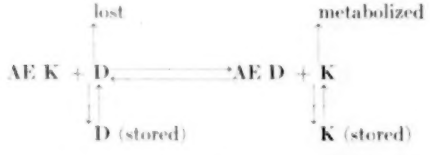
Dose of drug per Kg. of body weight†	*Dog*	*Time*					
		0	*1st day*	*2nd day***	*¼ hr.*	*6 hr.*	*24 hr.*
		Prothrombin time in seconds					
Vitamin K_1 10 γ	B	10	35	56	10	8	6
	M	8	24	36	13	9	6
Menadione 10 γ	B	7½	19	30	30	25	8
	M	7	18	27	24	16	7
Hykinone 6.1 γ	C	8	16½	26	22	11	7½
	M	7	13½	18	12	8	7½
Hykinone 16 γ	B	18	39	47	9	7	7
	M	8	19	16	9	7	7
Synkavite 9.4 γ	C	8	17	—	17½	12	8
	M	11	22	30	10½	9	7½

* A single dose of dicoumarin (1 mg. per Kg. of body weight) was injected.
† Only one dose was given.
** The vitamin K was given intravenously on the second day.

Discussion. The mode of action of dicoumarin in depressing the synthesis of prothrombin and its relationship to vitamin K have remained undetermined. In 1942 Witts[23] called attention to the basic similarity between the structure of 2-methyl-1,4-naphthoquinone and 4-hydroxy-coumarin, and he suggested that dicoumarin might act by blocking the utilization of vitamin K by the liver. Wooley[24] has also postulated that dicoumarin acts as an antivitamin. Although this concept is the most plausible one, various objections

have been made to it which Riggs[15] enumerates in a recent review.

The present findings support the concept that dicoumarin acts as an antivitamin. The fact that dicoumarin and vitamins antagonize each other, as demonstrated in this study, strongly suggests that both act on or through the same mechanism or agent. It has been postulated by the writers[13] that vitamin K acts as a prosthetic group which combines with an apoenzyme to form the active enzyme (AE K) which is responsible for the synthesis of prothrombin. This hypothesis may be further extended by assuming that dicoumarin may likewise combine with the apoenzyme to form AE D, which is not only inactive but also prevents vitamin K from forming the true holoenzyme. As a working guide, and only as such, the relation of vitamin K to dicoumarin may be expressed by the following scheme:



It has already been shown how stored vitamin K causes the organism to be refractory to dicoumarin. There is good evidence that dicoumarin can likewise be stored and that it can in this state oppose the action of vitamin K. Thorsen[22] reported that a patient who received 14 gm. of dicoumarin in 3 weeks developed a severe hemorrhagic state which continued for 3 weeks despite strenuous treatment before the prothrombin rose to a safe level. Several weeks later the prothrombin was again low and bleeding resumed even though no dicoumarin had been given after the first bleeding episode. Obviously, the drug remained in the body to inhibit the mechanism for the synthesis of prothrombin.

The organism's ability to excrete or destroy dicoumarin is an important factor. On the basis of earlier studies[12], it has been estimated that a normal dog can eliminate or inactivate a little less than 1 mg. per kg. of body weight daily. After liver damage, the animal's susceptibility to dicoumarin increases, due most likely to an impairment of the liver's function to inactivate the drug.

The relative affinity of vitamin K and dicoumarin is a determinant of the direction in which the reaction will proceed. Since 10 γ of vitamin K_1 can counteract 1000 γ of dicoumarin, it is obvious that the vitamin K has a much greater affinity for the apoenzyme. After a union of either vitamin K or dicoumarin has occurred with the apoenzyme, an excess of either agent is necessary to replace its opponent group.

The antagonistic actions of vitamin K and dicoumarin are probably not as simple as presented, but it seems reasonable to conclude that 3 major factors are involved: 1) the relative affinities of vitamin K and dicoumarin for the mechanism responsible for the synthesis of prothrombin; 2) the quantities of the 2 agents stored; and 3) the rate of elimination either by excretion, or by metabolic destruction or inactivation. The relative ineffectiveness of menadione to counteract dicoumarin may be explained by its weaker affinity for the apoenzyme, its poor storage, its rapid elimination, or a combination of either 2 or all 3 factors. The same considerations can be applied for the evaluation of potency to other drugs that have dicoumarin-like activity. Since menadione and other synthetic compounds having vitamin K activity are water soluble and probably are rapidly eliminated from the plasma, repeated administration of compara-

tively large doses as advocated by Shapiro and his associates[19] seems important to counteract the toxic action of dicoumarin. That synthetic vitamin K preparations are effective in correcting excessively prolonged prothrombin times caused by dicoumarin in man has recently again been shown by Overman *et al.*[9].

Summary. 1. After a cholecystnephrostomy, a dog's susceptibility to dicoumarin steadily increases which indicates that as the animal's store of vitamin K becomes depleted, dicoumarin becomes more effective in depressing the synthesis of prothrombin.

2. When dicoumarin and vitamin K are administered simultaneously in the ratio of 1 to 100 to a dog depleted of a vitamin K store, the 2 agents mutually oppose each other. Dicoumarin is prevented from causing a fall in the prothrombin level, while vitamin K is blocked from restoring the level to normal.

3. The marked hypoprothrombinemia produced by a small dose of dicoumarin is promptly corrected by vitamin K, somewhat less by Hykinone and Synkavite, and least effectively by menadione.

4. It is postulated that both vitamin K and dicoumarin have an affinity for the apoenzyme which is essential for the synthesis of prothrombin and that the following equilibrium occurs:

$$AE\,K + D \rightleftharpoons AE\,D + K$$

The factors which influence the equation are the relative affinities of dicoumarin and vitamin K for the apoenzyme, the store of vitamin K and dicoumarin in the organism, and the ability of the body to excrete or metabolically inactivate dicoumarin.

REFERENCES

1. **Boyd, E. J.,** and **Warner, E. D.:** J. Lab. & Clin. Med., **33**, 1431, 1948.
2. **Cromer, H. E.,** and **Barker, N. N.:** Proc. Staff Meet., Mayo Clinic, **19**, 217, 1944.
3. **Davidson, C. S.,** and **MacDonald, I. V.:** Am. J. Med. Sci., **205**, 24, 1943; New England J. Med., **226**, 353, 1943.
4. **Hawkins, W. B.,** and **Brinkhous, K. M.:** J. Exper. Med., **63**, 795, 1936.
5. **James, D. F., Bennett, I. L., Jr., Sheinberg, P.,** and **Butler, J. J.:** Arch. Int. Med., **83**, 632, 1949.
6. **Kapsinow, R., Engle, L. P.,** and **Harvey, S. C.:** Surg., Gynec. & Obst., **39**, 62, 1924.
7. **Lehmann, J.:** Science, **96**, 345, 1942.
8. **Miller, R., Harvey, P.,** and **Finch, C. A.:** New England J. Med., **242**, 211, 1950.
9. **Overman, R. S., Sorenson, C. W.,** and **Wright, I. S.:** J. Am. Med. Assn., **145**, 393, 1951.
10. **Overman, R. S., Stahmann, M. A.,** and **Link, K. P.:** J. Biol. Chem. **145**, 155, 1942.
11. **Quick, A. J.:** Am. J. Physiol., **118**, 260, 1937.
12. Idem: J. Biol. Chem., **161**, 33, 1945.
13. Idem: and **Collentine, G. E.:** Am. J. Physiol., In press.
14. **Quick, A. J.,** and **Stefanini, M.:** J. Biol. Chem., **175**, 945, 1948.
15. **Riggs, D. S.:** New England J. Med. **242**, 179 and 216, 1950.
16. **Roderick, L. M.,** and **Schalk, A.:** North Dakota Agricul. Exper. Station Bull., 250, 1931.
17. **Schofield, F. W.:** J. Am. Vet. M. A., **64**, 533, 1924.
18. **Shapiro, S., Redish, M. H.,** and **Campbell, H. A.:** Proc. Soc. Exper. Biol. & Med., **52**, 12, 1943.
19. **Shapiro, S., Weiner, M.,** and **Simson, G.:** New England J. Med., **243**, 775, 1950.
20. **Shoshkes, M., Geyer, R. P., Yee, G. S.,** and **Stare, F. S.:** J. Lab. & Clin. Med., **36**, 531, 1950.
21. **Smith, H. P., Warner, E. D., Brinkhous, K. M.,** and **Seegers, W. H.:** J. Exper. Med., **67**, 911, 1938.
22. **Thorsen, G.:** Lancet, **2**, 420, 1947.
23. **Witts, L. J.:** Glasgow Med. J., **19**, 57, 1942.
24. **Wooley, D. W.:** Physiol. Rev., **27**, 308, 1947.

RELATION OF 17-KETOSTEROID EXCRETION TO THE COMPLETENESS OF THE VIRILIZING SYNDROME

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In the course of an endocrine study on women and girls in which special attention was given to signs of masculinization, our data showed the usual association between various manifestations of virilism and the occurrence of elevated urinary 17-ketosteroid excretion. Since it also appeared that the level of this excretion tended to rise with the completeness of the virilizing syndrome, the data bearing on this point are herewith presented.

Methods of Study. Forty-two patients comprising the original study are elsewhere described in detail[2]. The 32 who are the subject of the present report are those in whom the 17-ketosteroid excretion was measured. They presented one or more of the following complaints: obesity, leanness, hirsutism, menstrual disturbance. There were other complaints irrelevant to this discussion. Racial composition was predominantly northwest European. Ages ranged from 14 to 49 years.

For purposes of this analysis we have considered the virilizing syndrome to embrace 3 main groups of symptoms: hirsutism, masculinization of body form, and menstrual disturbance.

Hirsutism is separated from masculinization, partly because hypertrichosis is just that common complaint the significance of which we hope the present considerations will help to appraise, and partly because it does indeed occur without other evidence of masculinity. By the same logic, we have made no separate rating of hypertrophy of the clitoris or deepening of the voice. These are rarely presenting complaints; where they are an expression of somatic virilism, they are most likely to occur along with other clear evidence of masculinization.

Masculinization of body form has been evaluated by criteria previously established, namely, by the assessment of androgyny[3]. On the basis of such assessments, patients were sorted into the following 7 groups: hyperfeminine, feminine, hypofeminine, hypobisexual (intermediate), bisexual, masculine, and disharmonious. For practical purposes the only difficult distinction is between underdevelopment and slight masculinity of body form. Frank overdevelopment and frank virilization are easy to identify. But the immature female form should not be confused with the form which has matured in the contrasexual direction; the hypofeminine body is "childish", not "boyish".

All patients in the hypobisexual (intermediate), bisexual, masculine and disharmonious groups were considered as showing some masculinization of body form.

Menstrual abnormality was rated as significant only where there was primary amenorrhea or secondary amenorrhea of more than a year's duration. The assumption is that the very presence of menstrual cycles, no matter how aberrant, testifies to a relatively more normal endocrine balance than is reflected in the absence of catamenia.

The excretion of 17-ketosteroids was measured according to Koets's modification[5] of the method of Robbie and Gibson[9]. The median normal range in Koets's laboratory for adult females is from 7 to 14 mg./24 hours, but readings are not considered definitely abnormal within the range from 5 to 18 mg./24 hours. The comparable broad normal male range is 7 to 27 mg. These norms are in agreement with those reported by Pincus[8].

Since the determinations in the present study were not made in any consistent relation

to the menstrual cycle, they were not analyzed as to individual rhythms, but the highest value found on any one patient was used for comparative purposes.

Findings. In looking for a relation between 17-ketosteroid excretion and clinical evidences of virilization, patients were sorted into groups according to which signs of virilism presented, and without regard to other symptoms or to over-all diagnosis. The results of this sorting are shown in Table 1. Fig. 1

TABLE 1.—17-KETOSTEROID EXCRETION (MG./24 HOURS) ACCORDING TO 3 SIGNS OF VIRILISM: HIRSUTISM, MASCULINIZATION, AMENORRHEA

	No Sign	*One Sign*			*Two Signs*		*Three Signs*
		hirsutism	*masculinization*	*amenorrhea*	*hirsutism, masculinization*	*masculinization, amenorrhea*	*hirsutism, masculinization, amenorrhea*
	7.5	6.7	7.5	15.5	14.4	10.4	65.8
	7.5	17.4	12.3	22.8	18.0	45.8	86.8
	7.5	18.7	14.5	28.9	24.6		293.0
	9.4	18.8	18.5		38.9		
	16.1	22.3	19.3		40.4		
	17.8	30.6					
	18.4						
	28.8						
Mean	14	19	14	22	27	28	149
Grouped mean	14		18			28	149

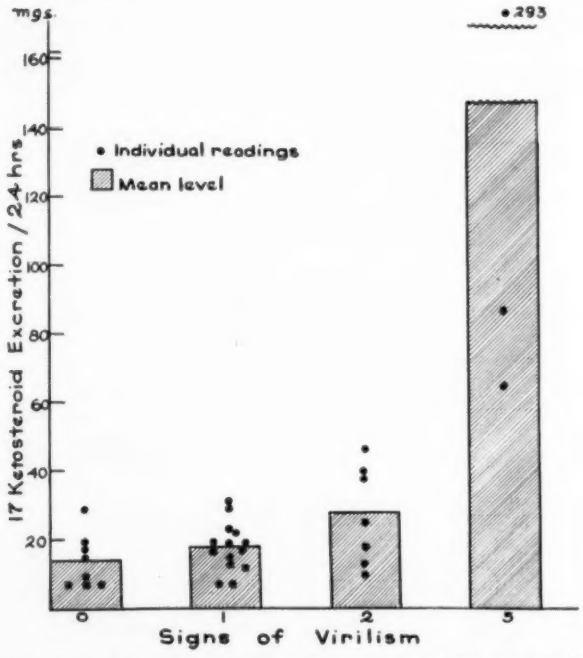
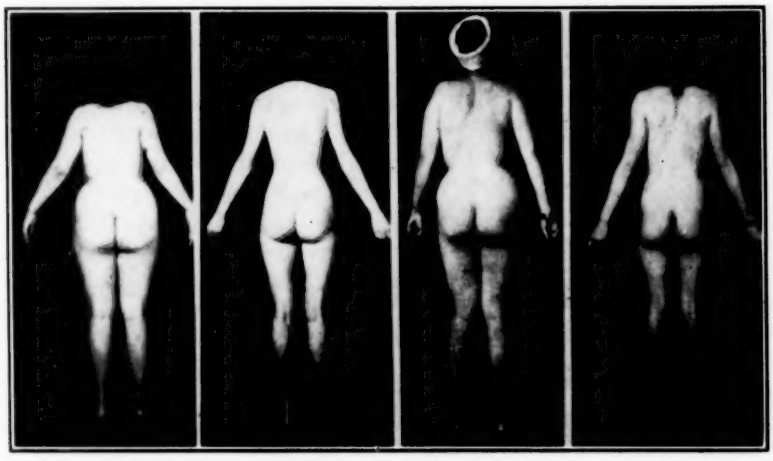


FIG. 1.—17-Ketosteroid excretion according to 3 signs of virilism; individual readings and means.

shows a pooling of the tabular material according to the number of signs present, without regard to their nature. Fig. 2 shows a characteristic patient from each group.

It is apparent that there is considerable overlap in 17-ketosteroid excretion between the groups, and a wide scatter in each. Even in the group with no sign of virilization there were several high readings. Nevertheless it excretion has not been analyzed. But it is well known that a degree of 17-ketosteroid elevation is found without virilization in such conditions as spondylarthritis and after Roentgen-radiation.

The completeness of the virilizing syndrome is thus related to the level of 17-ketosteroid excretion. This relation exists only within broad limits, of course, but is all the more note-



Signs of Virilism	None	One	Two	Three
Age in Years	19	26	17	17
Hirsutism	None	Marked	Moderate	Marked
Body Build	Feminine	Hypofeminine	Disharmonious (some masculinization)	Bisexual
Menses	Present	Present	Present	Amenorrhea
17 Ketosteroid Excretion	8	19	39	87

FIG. 2.—17-Ketosteroid excretion according to 3 signs of virilism; illustrative cases.

can be seen that with 1 sign, which might be any 1 of the 3, the readings ranged and averaged a little higher, with 2 signs they went still higher, but with 3 signs present the excretion rose sharply to the pathological range.

It should be emphasized that the group showing "no signs of virilization" were not otherwise normal; they were all patients with various somatic complaints. The possible relation of these complaints to their 17-ketosteroid

worthy in that there were many clinical variables in these patients besides their masculinization. The patient with the highest excretion (293 mg.) was a pseudohermaphrodite, the details of whose case were published in a separate report.[1]

Discussion. An increase in the production of androgen in the female expresses itself in many somatic effects, as well as by antagonizing both the production and action of estrogen. It

is therefore to be expected that both organic and functional evidences of masculinization will increase with the androgen level, as this is reflected in the rate of 17-ketosteroid excretion. This relationship might be more direct were there not great variations in the sensitivity of the end-organ systems involved, as well as in the total clinical picture. The latter, in turn, depends on the endocrine source of the androgen and on whatever other pathology may originate from the disturbed gland.

With regard to the symptom of hirsutism, Bissell[4] has reviewed the constitutional versus the humoral influences on hair growth. He concludes: "The constitutional factor is the capability of response of each individual follicle to endocrine stimuli. The humoral factor represents the various hormones supplying the stimulus for hair production to those follicles inherently sensitive to their action. Other local factors, such as follicular nutrition, nerve and blood supply must also exert their effect."

With regard to any parallel between the degree of virilization and the degree of 17-ketosteroid increase, both Bissell[4] and Luft[7] have made some observations. In his analysis of 33 hirsute women, Bissell identifies 29 as being idiopathic. Among these "the 17-ketosteroid excretion was normal or subnormal in the majority of the group". He did not find the level of 17-ketosteroid excretion to be helpful in etiological diagnosis. But he does report that "somewhat high values were found in four patients, all of whom showed severe virilizations," thus indicating a relation between 17-ketosteroid increase and degree of virilization.

In 14 cases of hirsutism, Luft[7] reported that according to his method "the andrin excretion was higher than in healthy women; it agreed with values found in healthy men." Furthermore, he reports, "There was a certain relation between the andrin excretion and the extension of masculine hair growth, the andrin excretion being higher in cases with more marked hair growth."

The elevation of 17-ketosteroid excretion in idiopathic hirsutism previously reported by Koets[6] is of a similar degree to the elevation here reported for similar cases, that is, elevations up to a maximum of 38 mg./24 hours. Since Koets's special observations were made in relation to the menstrual cycle, it is obvious they were made on women in whom the virilizing syndrome was incomplete, corresponding to our cases with "one or two signs."

Conclusion. In women and girls who present signs of virilization, there is a tendency for the level of 17-ketosteroid excretion to rise with the completeness of the virilizing syndrome. The complete syndrome is here considered as comprising hirsutism, masculinization of body form, and amenorrhea.

This parallel might be closer, were it not for constitutional and etiological differences in symptom production. Nevertheless, there is enough relation between clinical and laboratory findings so that the physician can anticipate with some accuracy in what range the 17-ketosteroid excretion will fall. He also has a basis for judging the probable significance of the laboratory finding. Particularly where hirsutism occurs alone, without masculinization of body form or cessation of menses, there can be a reasonable expectation that the symptom does not reflect serious pathology and that the 17-ketosteroid excretion will be only moderately elevated.

REFERENCES

1. **Bayer, L. M.**: Psychosom. Med., **9**, 246, 1947.
2. Idem, and **Reichard, S.**: Androgyny, Weight and Personality, Ibid., In Press.
3. **Bayley, N.**, and **Bayer, L. M.**: Am. J. Phys. Anthropol., **4**, 433, 1946.
4. **Bissell, G. W.**, and **William, R. H.**: Ann. Int. Med., **22**, 773, 1945.
5. **Davison, R. A.**, **Koets, P.**, and **Kuzell, W. C.**: J. Clin. Endocrinol., **7**, 201, 1947.
6. **Koets, P.**: Ibid., **9**, 795, 1949.
7. **Luft, R.**: Supplement 149, Acta med. Scandinav., 1944.
8. **Pincus, G.**: J. Clin. Endocrinol., **3**, 301, 1943.
9. **Robbie, W. A.** and **Gibson, R. R.**: Ibid., **3**, 200, 1943.

ON THE APPARENTLY ABSENT Q WAVE IN LEFT BUNDLE BRANCH BLOCK

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WILSON[14] was the first to stress the significance of an absent Q wave in both Lead I and his now conventional precordial leads derived from individuals with the electrocardiographic pattern of left bundle branch block. The presence of a Q wave in an electrocardiogram otherwise characteristic of left bundle branch block is regarded as most likely due to infarction of the interventricular septum. This firm belief is a rigorous logical conclusion of the dominant theory of the genesis of the electrocardiogram developed by Wilson himself.

According to this concept, a small Q wave over the left ventricle indicates that the left side of the septum is the first portion of the ventricular muscle to be activated. In left bundle branch block, the right side of the septum is initially activated, resulting in an initially positive deflection or R wave in leads facing the epicardial surface of the left ventricle. If the septum is infarcted, the subendocardial musculature of the right ventricle will be activated before that of the left ventricle, resulting in an initially negative deflection or Q wave in leads facing the epicardial surface of the left ventricle.

Untenability of Theory. This explanation of the significance of the presence or absence of a Q wave in left bundle branch block has proved extremely useful and appears to have considerable experimental and anatomic evidence for support. The evidence, by its very nature, must be circumstantial, at least to some extent, rather than direct and immediate. It would appear to be extremely difficult, if not impossible, to prove a direct relationship between the activation of a small segment of the myocardium and a portion of a picture of an electrical event which is one view of the resultant effect of the total electrical activity of the heart. On the other hand, factual observations that are contrary to theory cast doubt on its tenability. The two facts that caused the writers to question this theoretical explanation were 1) the character of the Q wave in left bundle branch block complicated presumably by septal infarction and 2) the fact that any specific precordial lead does not tap homologous portions of the myocardium in the normal heart and the heart with the electrocardiographic pattern of left bundle branch block.

It has been the experience of the authors and apparently that of others, as judged by illustrations in the literature, that when an electrocardiographic diagnosis of left bundle branch block with septal infarction is made on the basis of the presence of Q waves, the Q waves are usually slurred, notched, and broad. If these waves are due to unmasking activation of the free

wall of the right ventricle, they should be thin and of short duration because normal activation of the thin free wall of the right ventricle is a relatively fast electrical event. A slurred, notched, and broad wave derived from the free wall of the right ventricle is indicative of disease therein, a rather unusual sequel of infarction of the septum. This type of Q wave actually has all the characteristics of Q waves which have come to be recognized as characteristic of infarction in the absence of left bundle branch block.

More important is the fact that a specific precordial lead does not tap in the individual with left bundle branch block a portion of the myocardium that is homologous with the region of the heart tapped in the normal. Indeed, it is well known that there are individuals with normal hearts and with left ventricular hypertrophy who do not have Q waves in conventionally taken electrocardiograms. The explanation given for this is that the left ventricle is abnormally oriented with respect to the thoracic wall and that additional leads farther to the left, higher, or lower will display Q waves.

Moreover, there are instances of left bundle branch block without clinical or anatomic evidence of infarction which display tiny Q waves in Lead I. Sodeman, Johnston, and Wilson[11] reported such instances in which the clinical picture was not of a kind to expect septal infarction, and in one instance autopsy failed to show septal infarction. They stated that this type is rare and that it occurred in 8% of their series. The authors' experience indicates that it is much more common. Johnson *et al.*[5] recently reported its incidence as 19%. Sodeman[11] attributes such a Q wave to several possibilities: 1) transmission of initial positivity of the right ventricle to the right arm; 2) peculiarity of the Purkinje system or the architecture of the subdivision of the bundle branches and consequent change in the order of ventricular excitation; or 3) a combination of defects involving not only the left bundle but also other conducting tracts or the Purkinje network. Rosenman, Pick, and Katz[10] suggest as another possibility that the block may be below the normal left to right septal conduction.

Lastly, the differentiation between incomplete left bundle branch block and left ventricular hypertrophy, according to Wilson[14], may at times be impossible. More recently, Sodi-Pallares *et al.*[12] have suggested, from a study of left intracavity potential, that slurring of the ascending limb of the R wave in those leads reflecting the potential of the left ventricle is diagnostic of incomplete left bundle branch block whether a Q wave is present or absent. One wonders whether these explanations have a factual basis or are rationalizations of a theory.

Basis of Present Study. Cardiac enlargement involving predominantly the left ventricle is extremely common in left bundle branch block. Fahr[3], Rasmussen[7,8], and Master[6] relate the block to cardiac enlargement and myocardial damage. Rasmussen[9], on the basis of clinical and experimental evidence, believes that the pattern of left bundle branch block is an extension of the electrocardiographic pattern of left ventricular hypertrophy. For this reason, he proposes the term left ventricular retardation for both patterns. Because of the frequency of cardiac enlargement, it occurred to us that the presence or absence of a Q wave in left bundle branch block might be related to the orientation of the electrically active left ventricular myocardium to the thoracic cage.

Method and Material. Thirteen consecutive instances satisfying Wilson's criteria for left bundle branch block were selected for study.

Many electrocardiograms were discarded because of the presence of tiny but distinctly visible Q waves in Lead I. The heart was studied fluoroscopically to determine its relationship to the thoracic wall. In addition to the conventional precordial leads, leads encircling the entire thorax on a level with V_5, were obtained. Further, various other areas on the thorax, particularly the left posterior wall, were explored.

Results. Cardiac enlargement was present in each individual of this series. A typical example is shown in Fig. 1.

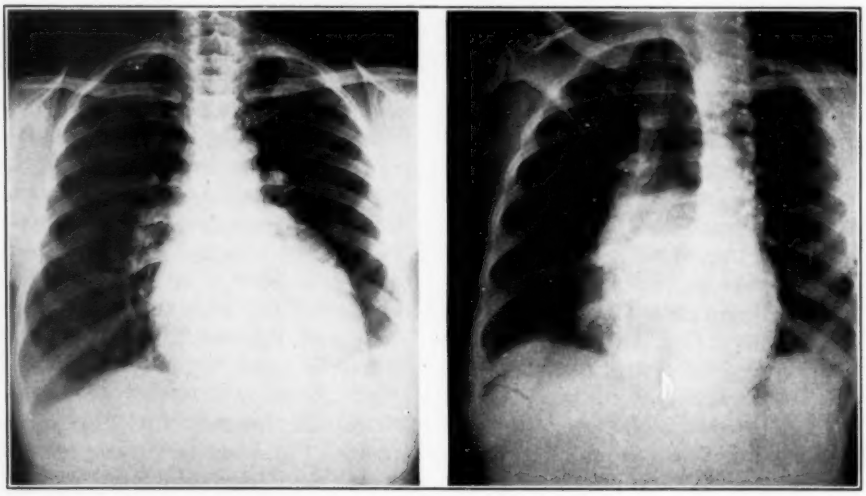

FIG. 1.—Reproductions of roentgenograms of Case 1, that of a 43-year old colored woman with rheumatic heart disease, in the (a, *left*) posterior-anterior view and (b, *right*) left anterior oblique view.

It can be seen that the enlargement involves predominantly the left ventricle which is situated more posteriorly than normal. The main bulge of the left ventricle is craniad to the left lower pole.

It would appear from the roentgenologic study that in these individuals a lead homologous with V_5 or V_6 in the normal would be approximately V_9 (mid-spinal line at T_7) or one taken 1 or 2 interspaces above V_9. Exploration of the entire thoracic wall in each instance revealed Q waves in the region of V_9, usually above V_9 and at times more to the right and at other times more to the left. A typical example is shown in Fig. 2.

Discussion. What is the significance of these Q waves? We cannot accept the theoretical explanation that they are cavity potentials because roentgenologic evidence does not support this assumption. Examination of Fig. 2 suggests a more plausible reason. One sees a gradual change in the direction of the complexes as exploration continues around the thorax. The positive ventricular complexes are derived from the left lateral and left posterior thoracic wall which are closest to the epicardial surface of the left ventricle. The negative ventricular complexes are derived from the right posterior, right lateral, and anterior thoracic wall, areas which are farthest from the epicardial surface of the left ventricle.

This relationship suggests that these leads represent different views of the total electrical field created by the

heart as a whole. This viewpoint is not new. It was first expressed by Bohning, Katz, and Langendorf[1] almost at the beginning of the clinical use of precordial leads. They stated that these leads gave information concerning the surface distribution of the electrical field created by the heart and did not require the assumption that any particular region of the heart determined the character of the deflections in any particular lead. Duchosal and Sulzer[2] initial portion of the central resultant electrical forces. Two of our cases are illustrated.

Case 1 is that of a 43-year-old colored female with rheumatic heart disease. The frontal, coronal, and sagittal plane characteristics of the spatial QRS vectorcardiographic loop are shown in Figs. 3, 4, and 5, respectively. From these loops, the presence, size, and duration of the Q waves can be predicted for any desired lead. This

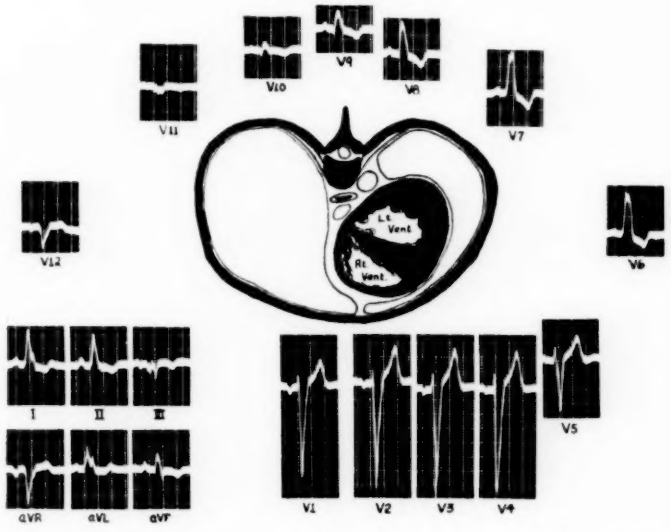

FIG. 2.—Electrocardiogram of Case 1 consisting of the standard and augmented unipolar limb leads, the conventional precordial leads, and other leads taken around the chest on a level with V_5, V_7 was recorded at the left posterior axillary line, V_8 at the left scapular line, V_9 at the mid-spinal line, V_{10} at the right scapular line, V_{11} at the right posterior axillary line, and V_{12} at the right mid-axillary line.

have shown that any lead can be derived from a spatial vectorcardiogram which appears to indicate that the dipole theory is applicable to the interpretation of precordial as well as extremity leads.

Because vectorcardiographic apparatus was not available to us, we used the method suggested by Grant[4] to determine the spatial QRS vectors and thereby ascertain whether the Q waves are simply different projections of the

is further illustrated by Figs. 6, 7, and 8 that represent the frontal, coronal, and sagittal plane characteristics of the spatial vectorcardiographic loop of Case 2, a 60-year-old white female with hypertensive heart disease. In the sagittal plane view, one can predict that the Q wave will be larger and the R wave will be smaller as the thoracic wall is tapped at areas above V_9. Three electrocardiograms taken above V_9 are shown to fulfill this prediction (Fig. 8).

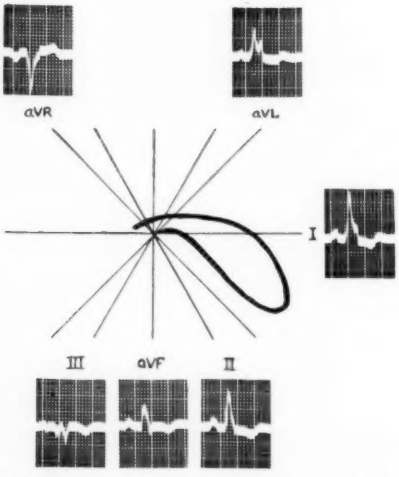

FIG. 3.—CASE 1. The spatial QRS vector loop in the frontal plane. The tracings represent the various leads and each is mounted on the positive side of the respective lead.

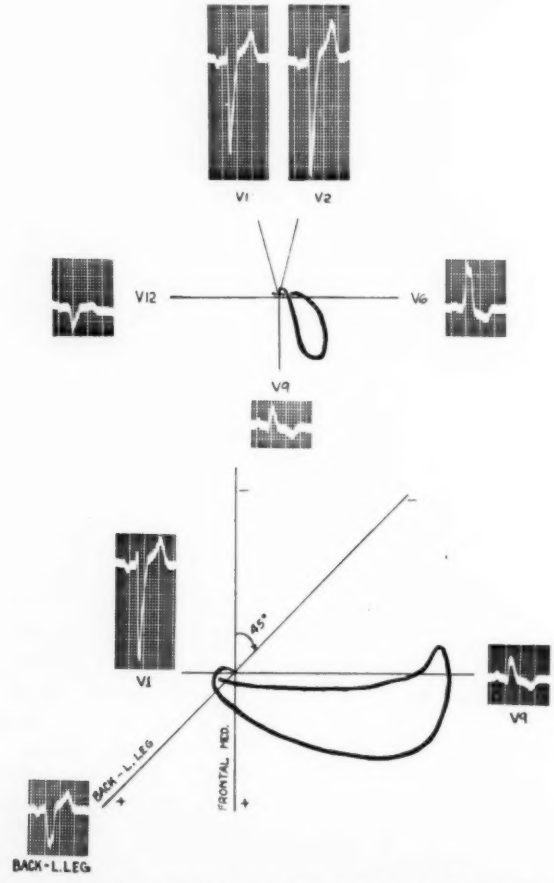

FIG. 4. *(Above.)*—Same: loop in coronal plane. FIG. 5 *(Below).*—Same: loop in sagittal plane.

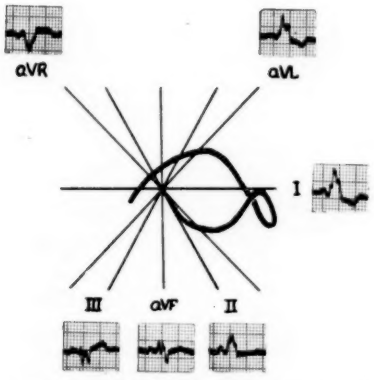

FIG. 6.—CASE 2. The spatial QRS vector loop in the frontal plane.

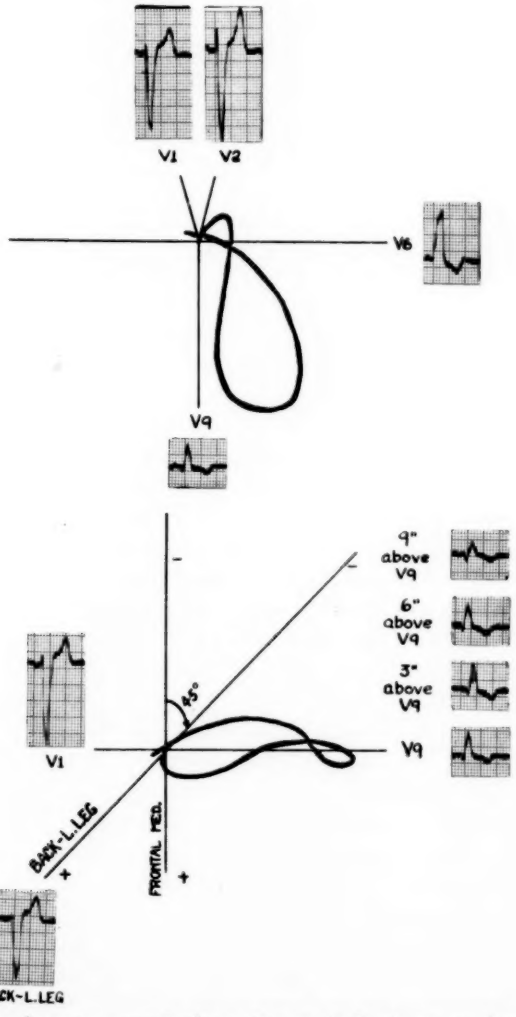

FIG. 7. *(Above).*—Same: loop in coronal plane. FIG. 5. *(Below).*—Same: loop in sagittal plane.

Similar predictions were made for other body surfaces and fulfilled by electrocardiographic tracings.

These findings appear to indicate that no special significance can be attached to this type of Q wave other than the orientation of the heart to the thoracic wall. It is possible that the electrocardiographic pattern of left bundle branch block with small narrow Q waves in Lead I or in Leads V_5 or V_6 occur in individuals with hearts that are more normally oriented to the chest wall. We purposely excluded this type of case because it did not fulfill the accepted criteria of left bundle branch block. Perhaps this is why all of the hearts in this series were very large.

The cause of this Q wave remains as uncertain as the cause of a Q wave in the normal electrocardiogram. Although it is customary to explain this wave as due to septal activation from left to right, Grant[4] claims to have correlated the initial part of the spatial vector that corresponds to the Q wave with the lie of the septum at postmortem examinations of a few subjects with normal hearts. He found the spatial vector at 0.04 second was more nearly parallel with the long axis of the septum than perpendicular. Unfortunately, he gives no information on the correlation of the spatial vector at 0.02 second with the lie of the septum.

Recent studies of intracavity potentials tend to support the theory of initial left to right septal activation in the normal because a QS deflection is obtained from the left ventricular cavity and an rS deflection from the right ventricular cavity. These results may be due to the orientation of the electrodes to the spatial vector of the heart rather than its position in one cavity or another. For, according to the dipole theory, proximity determines the magnitude but not the direction of the vector. Actually, rS patterns have been obtained from the left ventricular cavity[15] for which no satisfactory explanation could be given. Examination of the photograph showing the position of the cardiac catheters suggests to us the possibility that the electrode may have been on the positive side of the spatial vector.

On the other hand, leads tapping the epicardial surface of the left ventricle which have slurred, notched, and frequently widened Q waves with the electrocardiogram otherwise that of left bundle branch block have, in our experience and that of others, all had infarcts. The Q waves are identical in appearance with those characteristic of infarction in the absence of left bundle branch block. The authors regard this finding as a manifestation of focal myocardial block reported previously[13] as characteristic of the QRS complex in myocardial infarction. The block permits the uninfarcted left ventricular musculature to be activated earlier than that region surrounding the infarct. This phenomenon that was shown as a delay in the ascension of the R wave overlying the infarcted region is more clearly demonstrated by vectorcardiography. As Grant[4] pointed out, in normal subjects the 0.04 second spatial vector and the mean spatial vector are directed relatively parallel to each other but in infarction are opposite. This relationship holds true with or without left bundle branch block so that one mechanism is suggested, namely, earlier activation of the subendocardial uninfarcted musculature of the left ventricle.

Conclusions. 1. The presence or absence in any electrocardiographic lead of a smooth, thin narrow Q wave in left

bundle branch block depends upon the relation of this lead to the electrically active left ventricular musculature.

2. Slurred or notched Q waves, particularly those 0.04 second or longer in the electrocardiographic pattern of left bundle branch block in leads facing the epicardial surface of the left ventricle, are caused by focal block in the region of infarcted ventricular muscle.

REFERENCES

1. **Bohning, A., Katz, L. N.,** and **Langendorf, R.**: Am. Heart J., **22,** 778, 1941.
2. **Duchosal, P. W.,** and **Sulzer, R.**: La Vectorcardiographie, Basle and New York, S. Karger, 1949.
3. **Fahr, G.**: Arch. Int. Med., **25,** 146, 1920.
4. **Grant, R. P.**: Circulation, **2,** 676, 1950.
5. **Johnson, R. P., Messer, A. L., Shreenivas,** and **White, P. D.**: Am. Heart J., **41,** 225, 1951.
6. **Master, A. M., Kalter, H., Dack, S.,** and **Jaffe, H. J.**: Am. Heart J., **20,** 186, 1940.
7. **Rasmussen, H.**: Acta med. Scandinav., **110,** 32, 1942.
8. Idem: Ibid., **118,** 385, 1944.
9. Idem, and **Moe, T.**: Brit. Heart J. **10,** 141, 1948.
10. **Rosenman, R. H., Pick, A.,** and **Katz, L. N.**: Arch. Int. Med., **36,** 196, 1950.
11. **Sodeman, W. A., Johnston, F. D.,** and **Wilson, F. N.**: Am. Heart J., **28,** 271, 1944.
12. **Sodi-Pallares, D., Estandia, A., Soberon, J.,** and **Rodriguez, I.**: Am. Heart J., **40,** 655, 1951.
13. **Soloff, L. A.**: Am. Heart J., **40,** 839, 1950.
14. **Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossman, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R.,** and **Barker, P. S.**: Am. Heart J., **27,** 19, 1944.
15. **Zimmerman, H. A.,** and **Hellerstein, H. K.**: Circulation, **3,** 95, 1951.

BLOOD ERGOTHIONEINE LEVELS IN EUTHYROID AND HYPERTHYROID SUBJECTS

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Lawson and Rimington[5] reported in 1947 that ergothioneine (thioneine) has antithyroid properties. Because this substance is a naturally occurring component of whole blood, much interest has been aroused with regard to its possible significance in thyroid disease. Although other investigators[7,8] have failed to confirm the original conclusion, interest in the possibility of an inter-relationship of this substance and the thyroid gland has been kept alive by other reports. Pitt-Rivers[6] demonstrated an inhibition of the conversion of acetyldiiodotyrosine to acetylthyroxine by ergothioneine *in vitro*. Latner and Mowbray[4] found abnormally low values in 4 and low normal values in 2 cases of hyperthyroidism. Hunter's[2] lowest reported value was in a case of hyperthyroidism.

In addition to the above experimental observations, there are hypothetical considerations that point to a connection between thyroid activity and the function of ergothioneine. The pathological state of hyperthyroidism is characterized by acceleration of oxidation. It is reasonable to hypothesize that homeostatic mechanisms would tend to counter this increased oxidation. A readily available reducing agent might be expected to enter into this reaction. Ergothioneine, a reducing agent by virtue of its sulfhydryl radical, is a logical possibility, and furthermore, one might expect some alteration of circulating ergothioneine level as a result of such reaction. The report of Lawson and Rimington stimulated the present study which was undertaken to determine whether there was any measurable correlation between thyroid activity and blood ergothioneine levels.

Method of Study. All subjects studied were selected from the medical clinic or wards of the Wisconsin General Hospital, after history, physical examination, and other studies indicated into which category of thyroid function each case would fall. Nine patients were hyperthyroid, 21 were euthyroid, and 1 was myxedematous. Parallel measurements of radioiodine uptake* and protein-bound iodine by the method of Barker[1] were made in as many cases as possible in order to substantiate the clinical appraisal of altered thyroid function.

Procedure. The following procedure as described by Hunter[2] was used.

To 1.0 cc. of oxalated whole blood 9 cc. of 0.0045-N acetic acid–oxalate solution was added. The solution was thoroughly mixed with a stirring rod and then immersed in a beaker of faintly boiling water for 2 minutes to allow for coagulation of the protein. After centrifugation the supernatant was decanted into another tube. To the supernatant liquid 0.1 cc. of Goulard's extract was added followed by thorough mixing and centrifugation. This procedure removes the glutathione which would otherwise interfere with the final

* I^{131} used in this study was obtained from the Isotopes Division of the Oak Ridge National Laboratory of the Atomic Energy Commission, Oak Ridge, Tennessee.

analysis. Again the supernatant liquid was decanted and 0.1 cc. of 10% sodium dihydrogen phosphate solution was added which effects the removal of the excess lead. The liquid was again mixed and centrifuged. The supernatant was used as the test solution.

For each determination 1 cc. of test solution with 1 cc. of distilled water and 2 cc. of test solution, respectively, were added to Evelyn colorimetric tubes immersed in an ice bath. This afforded duplicate readings at varying ergothioneine concentrations. In rapid succession 1 cc. of diazo reagent and 2 cc. of an alkaline acetate buffer solution were added. Forty-five seconds were allowed for coupling, after which 5.0 cc. of 10-N sodium hydroxide were added. The tube was allowed to warm to room temperature and read in the colorimeter. A blank test was carried out using 2 cc. of distilled water in place of test solution to set the colorimeter at 100% transmittance.

The calibration curve is linear with a milligram/density slope of 0.045.

Results. Whole blood of 21 euthyroid subjects, 9 hyperthyroid subjects, and 1 hypothyroid subject was analyzed. The blood was drawn at random without regard to time of day or fasting state. Results are summarized in the accompanying table.

In the euthyroid subjects ergothioneine values varied from 1.35 to 4.5 mg./100 cc. with an average of 3.18 mg./100 cc. In hyperthyroid subjects the value varied from 1.40 to 5.8 with an average of 3.21. The single hypothyroid patient had a value of 3.3 mg.

Discussion. The report of Lawson and Rimington[5] indicating that ergothioneine has antithyroid activity was accepted with enthusiasm for two reasons: 1) it belongs to a group of chemicals with known antithyroid activity, and 2) it is a naturally appearing substance and therefore not apt to be provocative of untoward reactions with which the thiourea drugs have been associated.

Jackman *et al.*[3] examined the antithyroid activity of a large number of 4-alkyl derivatives of 2-mercaptoimidazole and found a wide range of activity. The activity exhibited by 4-N-

TABLE 1.—SUMMARY OF ANALYSES OF I^{131}, PROTEIN-BOUND IODINE AND ERGOTHIONEINE IN 31 SUBJECTS WITH VARIOUS THYROID STATES

Hyperthyroid				*Euthyroid*				*Hypothyroid*			
Case No.	I^{131}* (%)	*PBI* (γ *per 100 cc.*)	*Ergothioneine mg. per 100 cc.*	*Case No.*	I^{131} (%)	*PBI* (γ *per 100 cc.*)	*Ergothioneine mg. per 100 cc.*	*Case No.*	I^{131} (%)	*PBI* (γ *per 100 cc.*)	*Ergothioneine mg. per 100 cc.*
1.	70	11.	2.8	1.	28	4.5	1.35	1.	.7	5.8‡	3.3
2.	62	21.	1.4	2.	48	3.5	3.35				
3.	48	10.	3.5	3.	44	—	3.2				
4.	88	11.	4.1	4.	35	6.2	1.4				
5.	64	13.	5.8	5.	—	4.0	4.48				
6.	73	30.	3.8	6.	40	8.0	3.0				
7.	67	17.	1.9	7.	—	4.0	2.15				
8.	57	10.5	2.5	8.	18	4.0	4.35				
9.	70	16.2	3.1	9.	23	9.0	4.75				
				10.	40	5.0	4.20				
				11.	23	3.5	3.45				
				12.	56†	3.6	3.3				
				13.	55†	5.7	3.55				
				14.	—	—	3.2				
				15.	—	—	4.5				
				16.	—	—	3.75				
				17.	—	—	2.2				
				18.	—	—	3.1				
				19.	—	—	2.6				
				20.	—	—	2.0				
				21.	—	—	3.0				

*I^{131} indicates % uptake of test dose at 24 hours. A figure in excess of 50% is considered indicative of hyperthyroidism, provided the patient has not had prolonged propylthiouracil therapy.
†Two cases in which I^{131} uptake was elevated as a result of prolonged propylthiouracil therapy.
‡Normal. *PBI* in presence of clinical myxedema was ascribed to therapy with desiccated thyroid for several days prior to study.

• Dr. Pfiffner of Parke-Davis Co. kindly supplied ergothioneine used for standard.

propyl-2-mercaptoimidazole was 4 to 5 times that of thiouracil, while the very similar 4-N-amyl derivative was devoid of activity; 4-cyclohexylmethyl-2-mercaptoimidazole showed no activity, while benzl-2-mercaptoimidazole was at least as active as thiouracil. Ergothioneine, the methyl betaine of mercaptoimidazole, appears to belong to the inactive group.

At present there is no explanation for the conflicting data on the antithyroid activity of ergothioneine. However, most evidence indicates that this substance, in substantially larger doses than effective amounts of thiouracil, has no antithyroid activity.

From our data it would appear that there is no constant inter-relationship between the blood level of ergothioneine and thyroid activity.

Summary. 1) The reported evidence for a possible relationship between the thyroid state and blood ergothioneine levels is given.

2) Blood from 9 hyperthyroid subjects, 21 euthyroid subjects, and 1 hypothyroid subject was analyzed for ergothioneine by the method of Hunter.

3) No correlation between ergothioneine values and thyroid activity was established.

REFERENCES

1. **Barker, S. B.**: J. Biol. Chem., **173**, 715, 1948.
2. **Hunter, G.**: Canad. J. of Research E., **27**, 230, 1949.
3. **Jackman, M., Klenk, M., Fishburn, B., Miller, F.,** and **Archer, S.**: J. Am. Chem. Soc., **70**, 2884, 1948.
4. **Latner, A. L.,** and **Mowbray, R.**: Biochem. J., **42**, 35, 1948.
5. **Lawson, A.,** and **Rimington, C.**: Lancet, **1**, 586, 1947.
6. **Pitt-Rivers, R.**: Biochem. et Biophys. Acta, **2**, 311, 1948.
7. **Stanley, M. M.,** and **Astwood, E. S.**: Lancet, **2**, 905, 1947.
8. **Wilson, M.,** and **McGinty, D. A.**: Am. J. Physiol., **56**, 377, 1949.

EFFECT OF LARGE DOSES OF PROGESTERONE IN RHEUMATOID ARTHRITIS†

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The effect of cortisone (17-hydroxy-11-dehydrocorticosterone) in patients with rheumatoid arthritis[8] has been amply confirmed. The cost and untoward effects occurring during long periods of treatment, however, limit its effectiveness as a form of therapy for a chronic disease such as arthritis.

Because pregnancy[2] favorably affected rheumatoid arthritis, progesterone was suggested as an alternative therapeutic substance. In pregnancy, the production of progesterone is greatly increased[4,5], the peak being reached in the eighth month. At that time, the daily pregnanediol excretion which serves as a quantitative index of progesterone elaboration[8] reaches a peak of about 85 mg. This is a great increase over the normal nonpregnant pregnanediol excretion which is 1 to 4 mg. per 24 hours during the luteal phase of the menstrual cycle. It was thought that this increased progesterone elaboration during pregnancy might bear some relationship to the remissions seen at that time.

In addition, it has been observed that jaundice may also cause remissions in rheumatoid arthritis. It is known that the liver plays an important part in the inactivation of progesterone *in vivo*[6,7]. An intact liver will inactivate progesterone more efficiently than a damaged liver. Furthermore, progesterone metabolites[9] are excreted in bile. Thus the possibility arose that the beneficial effects of both pregnancy and jaundice might be due, at least in part, to an increase in circulating progesterone in the body.

Method. Eight patients with typical chronic active rheumatoid arthritis were studied. All but one, who was classed as "moderate," had "severe" arthritis of at least 1½ years' duration, as judged by the criteria of the American Rheumatism Association[18].

Six of the patients studied were hospitalized. Acetylsalicylic acid was not given during therapy, and the effect of hospitalization was minimized by allowing the patients to be ambulatory as much as possible. No physiotherapy was given during the period of treatment. All treatment was preceded by an observation period of 1 week to 2 months. Clinical assessment was made by one observer (P. J. V.). The range of joint motion was measured independently at regular intervals by a physiotherapist who did not know the plan of treatment.

Dosage. A dosage was selected which would be comparable to the progesterone production during pregnancy at the time most remissions occur. The production of progesterone as reflected in urinary pregnanediol excretion reaches 10 to 20 mg. per 24 hours at the end of the 1st period[4,5]. Most remissions of arthritis occur at this time, although some do not occur until the 5th month when pregnanediol excretion has increased to 40 mg. per 24-hour specimen. A nonpregnant woman given progesterone parenterally will excrete 10 to 15% as pregnanediol. To obtain

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pregnanediol excretion comparable to that seen in pregnancy, 200 mg. of progesterone daily by parenteral administration must be given. At present, only 3 patients with rheumatoid arthritis have been given treatment at this dosage level[11]. The dosages given our patients ranged from 200 to 500 mg. per day (Table 1).

Clinical Results. There was no striking, consistent improvement while patients were receiving large doses of progesterone. Five of the 8 patients showed varying degrees of improvement (Table 1). Only 1 patient, however, had marked improvement, while 2 others showed "moderate" and 2 "slight" improvement. The range of joint motion was slightly improved in 6 and moderate in 1 of the 8 patients. In general, the greater improvement was subjective and was associated with a moderate decrease in stiffness and pain during rest plus an increase in functional ability to perform manual tasks. There was less improvement in the objective signs of inflammation. It was noteworthy that despite subjective improvement during therapy there were intermittent evidences of activity, such as renewed aching at rest and new localized joint findings, such as swelling and heat. Improvement followed no definite pattern, occurring at any time during the 3 to 4 weeks of therapy. The patient's weight remained fairly constant.

There were no significant toxic manifestations associated with the administration of these relatively large doses. Withdrawal bleeding did not occur nor was there any fluid retention. The expected suppression of menstruation occurred during therapy and 1 patient (Case 4) after dosage averaging 400 mg. a day had 3 months of amenorrhea. Three patients noted somnolence while under treatment. Whether this was a manifestation of their disease or an effect of progesterone, cannot be definitely decided.

TABLE 1.—INFLUENCE OF PROGESTERONE IN RHEUMATOID ARTHRITIS

			Symptoms of Rheumatoid Arthritis		*Therapy with Progesterone*				*Sedimentation Rate (mm. in 1 hr.)*		*Weight (Kg.)*		*Cephalin Flocculation*	
Case	*Sex*	*Age*	*Duration (years)*	*Severity*	*Duration Days*	*Dose mg.*	*Degree of Clinical Improvement*	*Improvement in Joint measurement*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	F	19	3	Severe	17 13	100 200	Moderate	Slight	26	34	48.0	48.3	+	0
2	F	43	3½	Severe	3 26	300 200	Marked	Slight	42	38	55.8	56.0	++++	+++
3	F	59	33	Severe	2 28	300 200	Moderate	Slight	43	47	65.8	64.7	++++	+++
4	F	35	26	Severe	3 3 17 5	300 500 400 200	None	Moderate	38	39	58.1	56.0	+++	++++
5	F	17	4	Severe	3 22	300 200	None	None	36	39	—	—	+++	+++
6	F	44	1½	Severe	24	200	None	Slight	33	32	64.5	63.1	0	0
7	F	53	4½	Severe	21	200	Slight	Slight	37	46	53.8	53.3	+	0
8	F	33	3	Moderate	17	200	Slight	Slight	37	42	68.0	68.0	0	0

Laboratory Results. Clinical improvement was not associated with any change in the sedimentation rate (Wintrobe). All sedimentation rates were elevated prior to therapy and none showed a decrease.

Erythrocyte count, hemoglobin level, and leukocyte count were unchanged. The total urinary neutral 17-ketoste-

roids and corticoid excretions were followed in 6 patients. No consistent changes were seen during therapy with the exception of 1 patient (Case 2). This patient had a control 17-ketosteroid excretion of 2.4 mg. per day before treatment and an excretion of 8.4 mg. per day while receiving daily doses of 200 mg. of progesterone. When the dose was increased to 300 mg. per day, the 17-ketosteroid output increased to 11.1 mg. per day. This patient had a "marked" improvement during therapy.

The cephalin flocculation was 3 to 4 plus prior to therapy in 4 patients and remained unchanged.

The pregnanediol excretion was studied in 5 patients during progesterone therapy by the method of Venning[15,16]. The excretion varied (Table 2) between 10 and 80 mg. per day,

TABLE 2.—PREGNANEDIOL EXCRETION DURING PROGESTERONE THERAPY

	Case 1		*Case 2*		*Case 3*		*Case 4*		*Case 5*	
Day of treatment	*Amt. per day, mg.*	*% Recovered as pregnan.*	*Amt. per day, mg.*	*% Recovered as pregnan.*	*Amt. per day, mg.*	*% Recovered as pregnan.*	*Amt. per day, mg.*	*% Recovered as pregnan.*	*Amt. per day, mg.*	*% Recovered as pregnan.*
1	0		0		0		0		0	
2	0	3.7	0	1.0	0	0.4	0	1.5	0	2.6
3	0	mg./24 hr.	0	mg./24 hr.	0	mg./24 hr.	0	mg./24 hr.	0	mg./100 cc.
4	100		300		300		300		300	
5	100	20.0	300	15.7	300	9.0	200	12.0	300	14.0
6	100		300		300		200		300	
7	100		200		500		300		200	
8	100		200		500	13.8	200		200	
9	100		200		500		200		200	
10	100		200		400		200		200	
11	100		200		400	11.0	200		200	
12	100		200		400		200		200	
13	100		200		400		200		200	
14	100		200		400	17.5	200		200	
15	100		200		400		200		200	
16	100		200		400		200		200	
17	100		200		400	20.0	200		200	
18	100	32.0	200	22.5	400		200		200	
19	100		200		400		200		200	
20	200		200		400	17.1	200		200	
21	200		200		400		200	19.5	200	19.5
22	200		200		400		200		200	
23	200		200		400	14.0	200		200	
24	200		200		400		200		200	
25	200		200		400		200		200	
26	200		200		400		200		200	
27	200		200		200		200		200	
28	200		200		200		200		200	
29	200		200		200	40.5	200		200	
30	200	30.7	200	13.5	200		200	13.5	200	
31	200		200				200		200	

depending on the amount of progesterone used. With daily doses of 200 mg. the urinary pregnanediol averaged 37 mg. per 24 hours. This is comparable to urinary pregnanediol excretion in pregnancy up to the 5th or 6th month, by which time 90% of remissions in arthritis would have occurred. The percentage of progesterone excreted as pregnanediol varied between 9 and 40.5% although usually it was between 9 and 22%.

There was no significant change in total serum cholesterol, despite the relatively high steroid dose schedule. The concentrations of other blood constituents followed in serial manner were unchanged. This included blood urea nitrogen, fasting blood sugar, alkaline phosphatase, chlorides, serum proteins, thymol turbidity, calcium, and phosphorus.

Discussion. A review of the literature[10,11,14,19] and of our cases reveals that 55 rheumatoid arthritics have now been treated with progesterone, with varying results (Table 3). However, if all the cases are grouped as "effectively treated" if improvement was moderate or marked, and as "non-effectively treated" if improvement was no better than slight, only 43% of the male patients and 32% of the female patients were effectively treated. This improvement is no larger than might occur with other nonspecific forms of therapy. It certainly is not comparable to the results achieved with cortisone or ACTH therapy.

The case reports were examined statistically to ascertain whether there was any significant difference in response to therapy related to age or sex. No difference could be found in response between males and females or between premenopausal and postmenopausal ages.

The average daily dose of progesterone administered in previously reported cases varied usually between 50 and 100 mg. In this series of cases, daily injections of 200 mg. produced a urinary pregnanediol excretion of 37 mg. per 24 hours. This is comparable to the urinary pregnanediol excretion during pregnancy at the time remissions usually occur. Again, however, there was no significant difference between these treatment results and those obtained with smaller doses. This indicates that effective therapy cannot be achieved with progesterone by increasing the dosage, at least in the ranges used.

It becomes evident, then, that progesterone is of little benefit in the treatment of rheumatoid arthritis. This is particularly so if Freyberg's[3] three

TABLE 3.—INFLUENCE OF PROGESTERONE IN RHEUMATOID ARTHRITIS IN ALL REPORTED CASES SO TREATED

	Influence of Treatment				
Sex	*Marked*	*Moderate*	*Slight*	*None*	*Reference*
Men	2	4	4	2	14
	1	1		3	11
	0	1	1	1	10
	0	0	1	1	1
Women	2	3	0	4	14
	2	1	4	2	11
	0	0	3	1	10
	0	0	4	0	1
	1	2	2	3	This report
TOTAL CASES	8	12	19	17	

attributes of cortisone therapy are applied. These are: 1) dependability, 2) speed of action, and 3) the high degree of benefit obtained. It is important in evaluating any other compound's efficiency in arthritis to compare its effect with that of cortisone. Four of our 8 patients have been treated subsequently with cortisone with decidedly faster and more complete improvement. Whether the occasional improvements with progesterone represent the vagaries of the disease, or are due to an incomplete effect similar to that seen with suboptimal doses of cortisone, awaits further investigation.

It is possible that the minor relief obtained with progesterone may be a nonspecific steroid effect similar to the anesthetic effects of many steroid hormones, including progesterone, shown by Selye[15] in animal studies. In support of this possibility is the somnolence shown by 3 of our patients while receiving progesterone.

It has been reported by Sommerville *et al.*[17] that patients with rheumatoid arthritis excrete in the urine an abnormally high (19 to 36%) proportion of parenterally administered progesterone. This suggested a possible abnormality of steroid metabolism in rheumatoid arthritis. Two of the 8 patients in this study excreted over 20% of the administered progesterone. Because of the difference in methods of determining urinary pregnanediol and different dosage schedules, these data cannot be directly compared with the findings of Sommerville. As measured by urinary pregnanediol excretion, the dose of progesterone used in this study was comparable to the amount of circulating progesterone during pregnancy. Since no consistent improvement was seen, it is probable that progesterone is not solely responsible for the remissions during pregnancy. The relatively large amounts of progesterone administered with toxicity confirm the observations of Selye[15] in animals. He found that it was difficult to produce acute overdosage phenomena, even with the administration of 100 mg. of progesterone for a 100-gm. animal. The lack of progesterone toxicity is consistent with findings in other studies using progesterone in rheumatoid arthritis.

Summary. Eight patients with active rheumatoid arthritis were treated with large amounts of progesterone for 17 to 30 days. One patient showed a marked improvement associated with a 3 to 5-fold increase in neutral urinary 17-ketosteroid excretion. Moderate improvement was shown in 2 others and slight or no improvement in the others. In no case was there a decrease in sedimentation rate. Treatment with progesterone, even with the large doses employed, did not appear to be of any consistent benefit in rheumatoid arthritis. There were no toxic manifestations associated with the large dosage.

Progesterone (Proluton) was furnished by O. Edward Henderson, M. D., Director of Clinical Research of Schering Corporation, Bloomfield, New Jersey.

REFERENCES

1. **Alexander, W. R. M.**, and **Duthie, J. J. R.**: Lancet, **1**, 297, 1950.
2. **Browne, J. S. L., Henry, J. S.**, and **Venning, E. M.**: J. Clin. Invest., **16**, 678, 1937.
3. **Freyberg, R. H.**: Bull. of the New York Acad. Med., **26**, 206, 1950.
4. **Guterman, H. S.**: Progress in Clinical Endocrinology. New York, Grune and Stratton, 1950.
5. **Harris, T. N., Harris, S., Dannenberg, A. M., Jr.**, and **Hollander, J. L.**: Ann. Int. Med., **32**, 917, 1950.

6. **Hench, P. S.**: Proc. Staff Meet. Mayo Clinic, **13**, 161, 1938.
7. Idem: Arch. Int. Med., **61**, 451, 1938.
8. Idem, **Kendall, E. D., Slocumb, C. H.**, and **Polley, H. F.**: Proc. Staff Meet. Mayo Clinic, **24**, 181, 1949.
9. **Jones, G. E. S., Delfs, E.**, and **Stran, H. M.**: Bull. John Hopkins Hosp., **75**, 359, 1944.
10. **Kersley, G. D., Mandel, L.**, and **Jeffrey, M. R.**: Lancet, **1**, 703, 1950.
11. **Kyle, L. H.**, and **Crain, D. C.**: Ann. Int. Med., **32**, 878, 1950.
12. **Masson, G.**, and **Hoffman, M. M.**: Endocrinol., **37**, 111, 1945.
13. **Pearlman, W. H.**, and **Cicero, E.**: J. Biol. Chem., **176**, 847, 1948.
14. **Reich, N. E.**: Amer. Prac. **4**, 1, 1949.
15. **Selye, H.**: Proc. Soc. Exper. Biol. & Med., **46**, 116, 1941.
16. Idem, and **Stone, H. J.**: J. Pharmacol. & Exp. Therap., **80**, 386, 1944.
17. **Sommerville, I. F., Marrian, G. E., Duthie, J. J. D.**, and **Sinclair, R. J. D.**: Lancet, **1**, 116, 1950.
18. **Steinbrocker, O., Traeger, C. H.**, and **Batterman, R. C.**: J. Am. Med. Assn., **140**, 659, 1949.
19. **Touw, J. F.**, and **Knipers, R. K. W.**: Acta Med. Scandinav., **96**, 501, 1938.
20. **Venning, E. H.**: J. Biol. Chem., **119**, 473, 1937.
21. Idem: Ibid., **126**, 595, 1938.

EFFECTS OF DIOXYLINE PHOSPHATE AND ENTERIC-COATED KHELLIN ON CORONARY ARTERY INSUFFICIENCY

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THERE has long been a general lack of accord as to the usefulness of certain drugs in the treatment of pain in patients with angina pectoris. Khellin[1,2,14] (Visammin), papaverine[6], and the xanthines[11] have been regarded by some as useful in the treatment of coronary artery disease. It has been suggested that these drugs would be of aid in the prevention or reduction in the number or severity of anginal attacks when administered orally throughout the day. In general, however, this plan of treatment has been unsatisfactory[7,8,9] either because of doubtful value of the drug or of an inability of many patients to tolerate an adequate amount of the particular drug due to severe side-effects. We have recently studied a synthetic papaverine-like drug and an enteric-coated form of khellin in order to determine their clinical effectiveness and side effects in the treatment of angina pectoris.

Dioxyline phosphate* is a synthetic compound similar to papaverine in chemical structure and physiological activity. Chemically it is 6, 7-dimethoxy-1 - 4′ - ethoxyl - 3 - methoxybenzyl - 3-methyl-isoquinoline. The drug has been shown to cause coronary dilatation of a degree and duration equal to that of papaverine when equal amounts are injected in dogs[10].

Toxicity studies in albino mice suggest the drug to be less toxic by the oral route or intravenous injection than papaverine hydrochloride[10]. Studies in man following intravenous injection of dioxyline phosphate show no significant alteration in cardiodynamics[4].

Khellin** (Visammin) is chemically 2 - methyl - 5, 8 - dimethoxy-furanochromone. The enteric coating applied to the drug was of the cellulose acetate phthalate type. Data supplied by the manufacturer indicate the coating will remain intact up to 5 hours in the stomach but will disintegrate within 1 hour after passing the pylorus. The usual sugar coating will dissolve within 10 minutes in the stomach. The tablets themselves will disintegrate in 20 to 30 minutes.

The present study was undertaken to determine if preparation of a synthetic analogue of papaverine or the addition of an enteric coating to khellin would minimize side-effects to the extent that an optimal therapeutic dose

* Dioxyline phosphate (Paveril phosphate) was generously supplied by Dr. Kenneth G. Kollstaedt of the Eli Lilly Co., Indianapolis, Indiana.

** Khellin (Eskel, enteric coated) was generously supplied by Mr. William M. Swain of Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania.

could be tolerated by the patient. The previously reported method[3] of utilization of the ability of a drug to prevent electrocardiographic changes in a group of tests of coronary insufficiency was employed as an objective criterion of drug effect.

Method. SELECTION OF PATIENTS. Studies were made in a group of 11 patients with arteriosclerotic disease of the coronary arteries. Classical angina pectoris consisting of exertional substernal pain with typical radiation relieved promptly by rest had been present for at least 2 years. There was no evidence of anemia, hyperthyroidism, congestive heart failure, or recent myocardial infarction in any of the patients.

Initially all patients received a complete physical examination, blood count, and roentgenogram of the chest. Exercise tolerance, anoxemia, and ergonovine tests for coronary insufficiency were then performed. In all patients at least 2 of these 3 tests were consistently positive. The testing procedures were performed at the same time each day, and no more than 1 test was performed on any day.

The patients were instructed as to the planned procedure with special emphasis on the use of a daily diary in which was recorded the number of nitroglycerine tablets required while undertaking their usual activities. Only patients who were thought to be co-operative and of adequate intelligence were included. All patients remained ambulatory and continued their usual activities throughout the study.

MEDICATION. Three materials were compared in this study: dioxyline phosphate 1.2 gm. per day, enteric-coated khellin, 120 mg. per day, and inert lactose placebo tablets indistinguishable in shape, size, and color from the active medications. All tablets were given in divided doses 3 times a day before meals.

There was an initial control period during which no medication was given and then each of the following drugs was studied for a 5-week period: dioxyline phosphate, dioxyline phosphate-like placebo, enteric-coated khellin, and enteric-coated khellin–like placebo. The patients took nitroglycerine as needed through all periods of study. The order of administration was varied from patient to patient and was unknown both to the patient and to the examiner. Finally in the event the electrocardiographic tests remained positive following oral dioxyline phosphate treatment, they were repeated following a single injection intravenously of 200 mg. of the drug.

ELECTROCARDIOGRAPHIC EVALUATION. 1. *Exercise Tolerance Test, Method of Masters and Associates*[13]: The patients rested 15 minutes, then performed the graded exercise on standard steps as indicated by tables based on sex, age, and weight. The exercise was completed in 1½ minutes. An electrocardiogram consisting of leads I, II, III, and V_4 was recorded before exertion and this was repeated immediately on cessation of exercise and at intervals of 3, 5, and 8 minutes thereafter. In the event of pain, an immediate electrocardiogram was taken and nitroglycerine, 0.43 mg., was given sublingually.

Criteria for a positive test consisted of a depression of the RS–T junction of at least 1 mm. in any lead, conversion of an upright T wave to an iso-electric or inverted T in lead I, II, or V_4. The conversion of an inverted T to an upright T was considered an abnormal response.

2. *Anoxemia Test, Method of Levy and Co-workers*[12]: A reduced oxygen mixture consisting of 10% oxygen and 90% nitrogen was administered by means of the McKesson gas machine which was equipped with a flutter valve so that no rebreathing of the mixture occurred. Periodic determinations of the gas mixture by the method of Haldane showed it to be constant 10 ± 0.02% oxygen. A control electrocardiogram consisting of leads I, II, III, and V_4 was initially recorded. The reduced oxygen mixture was then given for 20 minutes, during which time electrocardiograms were repeated at 5-minute intervals and for 15 minutes following the completion of the gas administration. In the event of pain an immediate electrocardiogram was taken and 100% oxygen given by inhalation.

Criteria for a positive test were similar to those described by Levy, that is, the sum of the RST depression in all leads exceeds 3 mm., or the direction of the T wave in leads I and V_4 is reversed, accompanied by a depression of 1 mm. or more of the RS-T complex.

3. *Ergonovine Test, Method of Stein*[15]: A control electrocardiogram consisting of leads I, II, III, and V_4 was recorded following a 15-minute rest period. Ergonovine maleate, 0.2 mg., was injected undiluted into an antecubital vein. Repeated electrocardiograms were recorded at intervals of 5 minutes for 1 hour. In the event of any pain an immediate electrocardiogram was taken and nitroglycerine was given.

Our criteria for a positive test consisted of a depression of the RST segment of 1 mm. in the limb leads or of 2 mm. in the V lead or inversion of a previously upright T wave in leads I, II, or V_4.

Symptomatic Improvement. All patients were seen at weekly intervals by 1 or 2 examiners who were unaware of the medication given at the last visit. They were questioned as to daily requirements of nitroglycerine and severity of anginal attacks. Symptomatic improvement was considered to have occurred if the patient required less than 50% of the number of nitroglycerine tablets taken during the control period and if he or she spontaneously reported reduction in the number or severity of the anginal attacks.

Eleven (35.4%) reverted to normal following oral therapy of dioxyline phosphate. An additional 3 tests became normal following intravenous injection of the drug. Thirteen tests (41.9%) reverted to normal following enteric-coated khellin. All tests returned to the pre-treatment status following placebo therapy. Patient B. M. was unable to perform the exercise tolerance test because of severe rheumatoid arthritis.

Occurrence of Pain During Testing. Precordial pain occurred in 24 (75%) of the 32 tests during pre-treatment testing. Similar pain occurred on 15 (46.9%) occasions following dioxyline phosphate and on 17 (53.3%) occasions following enteric-coated khellin.

TABLE 1.—EFFECTS OF DRUGS ON ELECTROCARDIOGRAPHIC TESTS FOR CORONARY INSUFFICIENCY

	Exercise Tolerance Test			*Anoxemia Test*			*Ergonovine Test*		
Patient	*Control**	*Dioxyline Phosphate*	*Enteric Khellin*	*Control**	*Dioxyline Phosphate*	*Enteric Khellin*	*Control**	*Dioxyline Phosphate*	*Enteric-Coated Khellin*
G. A.	+	⊕	−	+	−	−	+	−	+
H. F.	+	−	+	+	+	+	−	−	−
H. M.	+	−	−	+	⊕	−	+	−	−
H. L.	+	+	+	+	+	+	+	+	+
S. M.	+	+	−	+	+	+	+	−	−
B. S.	+	−	−	+	⊕	+	+	−	−
C. E.	+	+	+	+	+	+	+	+	+
D. M.	+	+	+	+	+	+	+	−	+
B. M.	○	○	○	+	+	+	+	−	−
H. T.	+	+	+	+	+	+	+	−	−
H. J.	+	+	−	+	+	+	+	+	−

\+ Positive Test
− Negative Test
○ Test Not Performed
⊕ Became Negative Following Intravenous Drug
* Placebo and Control Results were Identical

Toxic Symptoms. The appearance of anorexia, nausea, vomiting, or diarrhea was considered to be a drug effect if it occurred while the patient was receiving the drug and ceased following the temporary substitution of placebo tablets.

Results. Effect on Electrocardiographic Tests. The response of the patients to exercise tolerance, anoxemia, and ergonovine tests is shown in Table 1. Thirty-two tests were performed prior to treatment. Thirty-one (96.9%) of these tests were positive.

Symptomatic Response. Reduction in number and severity of the anginal attacks and 50% reduction in average nitroglycerine consumption occurred in 7 patients while on enteric-coated khellin, in 6 patients while on dioxyline phosphate, and in 1 patient while

on placebo tablets. These results are shown in Table 2.

Toxic Symptoms. Anorexia, nausea, vomiting, and diarrhea were the principle toxic symptoms. Their occurrence is shown in Table 2. In general, the use of enteric-coated khellin was greatly limited by the severity of the toxic effects, whereas the use of dioxyline phosphate was accompanied by only mild toxic manifestations.

Discussion. Angina pectoris is generally thought to be due to a relative disproportion between the demands of the myocardium for oxygenated blood and the supply of such blood available through the coronary arteries. It may be due to an inability of arteriosclerotic vessels to dilate[5], but some degree of vasospasm is suggested by the classical response to the short-acting nitrites.

Many drugs have been recommended for clinical use in the treatment of angina pectoris on the basis of experimental studies in the dog which suggest that they may increase coronary blood flow. With the exception of the short-acting nitrites, the coronary vasodilator drugs have been disappointing in the human. This may be due to obvious differences in the character and distribution of the coronary vessels in the dog as compared to the arteriosclerotic human. It would be highly desirable to be able to measure directly coronary blood flow in man during increasing amounts of myocardial demand. Due to the unavailability of such a direct method, the authors have accepted the electrocardiogram as a useful indirect means of studying the adequacy of the coronary circulation. The use of more than one type of test is desirable in the evaluation of a drug. The ergonovine test appears to be more easily reversible with drug therapy than either the exercise tolerance or anoxemia tests.

TABLE 2.—EFFECT OF DIOXYLINE PHOSPHATE AND ENTERIC-COATED KHELLIN IN 11 PATIENTS

	Symptomatic Improvement			*Toxic Symptoms*		
Patient	*Placebo*	*Dioxyline Phosphate*	*Enteric-Coated Khellin*	*Placebo*	*Dioxyline Phosphate*	*Enteric-Coated Khellin*
G. A.	No	Yes	Yes	No	No	Yes
H. F.	No	No	No	No	Yes	Yes
H. M.	No	Yes	Yes	No	No	No
H. L.	No	No	No	No	No	Yes
S. M.	No	Yes	Yes	No	Yes	Yes
B. S.	No	Yes	Yes	No	No	No
C. E.	Yes	Yes	Yes	No	No	Yes
D. M.	No	No	No	No	No	Yes
B. M.	No	No	No	No	Yes	Yes
H. T.	No	Yes	Yes	No	No	No
H. J.	No	No	Yes	No	No	Yes

The data would seem to indicate that both dioxyline phosphate and enteric-coated khellin may be helpful in preventing myocardial anoxia in certain patients with coronary arteriosclerosis. The action is presumably that of vasodilation of the collateral coronary vessels sufficient to permit more blood to reach anoxic areas of the myocardium.

Subjective improvement is very difficult to evaluate in any disease, and this is particularly true in arteriosclerotic coronary artery disease. However, the majority of the patients used less nitroglycerine and tolerated activity

better while taking the drugs as compared to placebo and control periods.

Toxicity is a major problem with khellin therapy. It would seem that the use of an enteric coating does not decrease the occurrence or severity of toxic symptoms.

Diarrhea occurred only with the enteric-coated khellin.

Two patients (C. E. and H. L.) died of myocardial infarction while on placebos at the completion of the drug therapy. It was thought in these 2 instances that death was not directly related to the previous drug therapy.

The drugs seem to be equally effective in the treatment of angina pectoris in this small series of patients. However, individual patients seem to vary as to responsiveness to each drug. Clinically it may be wise to try both drugs and select the one that is best tolerated at a therapeutic level.

Summary. 1. The effects of dioxyline phosphate and enteric-coated khellin were studied in 11 patients with severe angina of effort.

2. Thirty-one of 32 (96.9%) electrocardiographic tests for coronary insufficiency performed prior to treatment showed consistent abnormalities.

3. Normalization occurred in 11 (35.4%) tests following administration of oral dioxyline phosphate and 13 (41.9%) following use of enteric-coated khellin.

4. Symptomatic improvement followed the use of dioxyline phosphate in 6 patients and after enteric-coated khellin in 7 patients.

5. Toxic side effects occurred in 3 patients following administration of dioxyline phosphate. Side effects of greater severity followed the use of enteric-coated khellin in 8 patients.

6. It would seem that further experimental and clinical studies are warranted in regard to use of both dioxyline phosphate and enteric-coated khellin in the treatment of angina pectoris.

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REFERENCES

1. **Anrep, G. V., Kenawy, M. R.,** and **Barsoum, G. S.:** Am. Heart J., **37,** 531, 1949.
2. **Armbaust, C. A.,** and **Levine, S. A.:** Am. J. Med. Sci., **220,** 127, 1950.
3. **Best, M. M.,** and **Coe, W. S.:** Circulation, **2,** 344, 1950.
4. Idem: Unpublished Observations.
5. **East, T.:** Cardiovascular Disease in General Practice, Philadelphia, The Blakiston Company, 1949, p. 67.
6. **Elek, S. R.,** and **Katz, L. N.:** J. Am. Med. Assn., **120,** 434, 1942.
7. **Evans, W.,** and **Hoyle, C.:** Quart. J. Med., **26,** 311, 1933.
8. **Gold, H., Kwit, N. T.,** and **Otto, H.:** J. Am. Med. Assn., **108,** 2173, 1937.
9. **Greiner, T., Gold, H., Cattell, M., Travell, J., Bakst, H., Rinzler, S., Benjamin, Z., Warshaw, L., Bobb, A., Kwit, N., Modell, W., Rothendlar, H., Messeloff, C.,** and **Kramer, M:** Am. J. Med., **9,** 143, 1950.
10. **Henderson, F. G., Shipley, R. E.,** and **Chen, K. K.:** To be published.
11. **Le Roy, G. V.:** J. Am. Med. Assn., **116,** 921, 1941.
12. **Levy, R. L., Bruenn, H. A.,** and **Russell, N. G.:** Am. J. Med. Sci., **197,** 241, 1939.
13. **Master, A. M., Friedman, R.,** and **Dack, S.:** Am. Heart J., **24,** 777, 1942.
14. **Rosenman, R. H., Fishman, A. P., Kaplan, S. R., Levin, H. G.,** and **Katz, L. N.:** J. Am. Med. Assn., **143,** 160, 1950.
15. **Stein, I.:** Am. Heart J., **37,** 36, 1949.

THE INFLUENCE OF MATERNAL AND OBSTETRICAL FACTORS ON FETAL SURVIVAL

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Several previous papers on neonatal mortality have given the impression that fetal factors, such as weight and degree of maturity, are the most important[2,7]. In this survey, we will consider several maternal and obstetrical factors that have a very definite effect on fetal survival. The period of study extends for 30 months, during which time 3751 deliveries were completed. Excluded from the study are the previable infants: namely, those weighing less than 1000 gm.[9]. Neonatal deaths and stillbirths are treated as one problem. It is our feeling that, with some few exceptions, the obstetrician is responsible for all untoward results. Both premature and mature infants are considered as one group, for the diagnosis of prematurity alone was made in only 3 instances.

Methods. The diagnosis of prematurity and immaturity is a matter of some controversy. Methods developed for diagnosis are often involved and cumbersome[3,6]. They have employed gestational age, weight, length, circumference of head and thorax, and computations of surface area. At this institution the division into premature and mature infants is made entirely on a weight basis. Infants weighing less than 1000 gm. are classed as pre-viable, those of 1000 to 2500 gm. as premature, and those over 2500 gm. as mature. Such an arbitrary stand will exclude some premature or immature infants weighing over 2500 gm., and will include some mature infants that weigh less.

The procedure for handling the mother and infant in premature labor is fairly well defined. The administration of sedatives is held to a minimum. The usual regimen is demerol 50 mg. and scopolamine 0.3 mg. as a single dose, or the scopolamine alone in similar dosage. Frequently no sedation is given in the first stage of labor. This may be accomplished by carefully explaining the situation to the mother, and by proper psychological preparation for the onset of labor. Delivery anesthesia is varied. Low spinal, saddle block, pudendal block, and infiltration of the perineum with local anesthetics are used. The use of inhalation anesthesia is rare. An incubator is kept in the delivery room, with immediate transfer of the infant to the premature nursery. In mature infants, demerol, 100 mg., and scopolamine, 0.4 mg., are used. They are repeated at 4-hour intervals as needed. Sedation in the case of the term infant is minimal when compared with that used in other institutions. For delivery anesthesia, all the above methods, plus drop ether,

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are used. We are all greatly concerned about the amount of sedation used in a premature infant. Unfortunately, too little thought is given to the possible long-range effects of excessive sedation on the term infant.

Results in 3751 Cases. As stated, there were 3751 deliveries. Of this total, 267 were premature infants. The incidence of prematurity is 7.1%. This is a relatively low figure, as the incidence reported from other clinics varies from 7 to 13%[10,13,15]. The infants were then grouped by weight. Group 1 consists of those weighing from 1000 to 1500 gm.; Group 2, from 1500 gm. to 2000 gm.; Group 3, from 2000 to 2500 gm.; and Group 4, those exceeding 2500 gm. Thus the division by weight is shown in Table 1.

Neonatal death in this survey totaled 70, and the number of stillbirths was 64. Thus, the uncorrected fetal loss is 3.5%. This seems to indicate that being born is the most hazardous period of one's life. Further study reveals that Group 1, with 1% of births, had 24.3% of the deaths. Group 2, with 1.3% of births, had 7.1% of deaths. For the largest number of prematures, Group 3, the findings are 4.7% of all births, and 5.7% of deaths. In the term infants, 92.9% of the births and 62.8% of the deaths were noted. In the stillborn infants, Group 1 and 2 had 15.6% each, Group 3 had 9.5%, and the term infants had 59.3%. Tables 2 and 3 list the number of deaths and their several causes.

TABLE 1.—WEIGHT DISTRIBUTION OF 3751 INFANTS AT BIRTH

Group	*Number of Infants*	*Percentage of Prematures*	*Percentage of all Births*	*Deaths*	*Mortality Percentage*
1	38	14.2	1.0	27	71.0
2	49	18.3	1.3	15	30.6
3	180	67.4	4.7	10	5.5
4	3484		92.9	82	2.2

TABLE 2.—CAUSES OF DEATH IN 64 STILLBIRTHS AMONG 3751 INFANTS

Factor	*Group One*	*Group Two*	*Group Three*	*Group Four*	*Total*
Congenital anomalies incompatible with life	6	1	1	7	15
Asphyxia (delayed breech)	1	0	0	2	3
Asphyxia (prolapsed cord)	0	2	0	4	6
Asphyxia (abruptio)	0	1	2	4	7
Atelectasis	1	5	0	1	7
Erythroblastosis	0	0	0	3	3
Unknown	1	0	1	5	7
Birth trauma	0	0	0	3	3
Pre-eclampsia	1	1	1	4	7
Syphilis	0	0	1*	3	4
Intra-partum infection	0	0	0	2	2

Analysis of Results. Consideration of factors involved in infant non-survival reveals that 32 had congenital anomalies incompatible with life. Obviously, little can be done to combat this condition. Of interest are 2 findings. In 3 of the cases, previous delivery had produced malformed infants. Four other patients had signs and symptoms usually associated with threatened abortion. Viral infections, particularly

German measles[8], have been reported as an etiological agent. In this series, such infections were conspicuous only by their absence.

The second largest group is that of trauma associated with labor and delivery. Of the 21 reported, 8 cases occurred in breech delivery, and 4 were associated with midforceps procedures. Four were noted in low or outlet forceps maneuvers, and the remainder in spontaneous deliveries. Rapid labor may have been responsible for 2 of the latter cases. The finding of laceration of the vein of Galen with sub-tentorial or sub-arachnoid hemorrhage was noted most frequently after breech delivery. With midforceps, subarachnoid or petechial hemorrhages were noted throughout the brain substance. Therefore it is clear that delivery of an infant presenting as breech is a most hazardous procedure. First, the unmolded head must rapidly fit into the pelvis. Secondly, in prematures below the 34th week of gestation, the circumference of the head still exceeds that of the shoulders. It is easily understood how the head could be trapped in an incompletely dilated cervix. Additional cases of fetal mortality from breech delivery are discussed under the diagnosis of asphyxia.

There is a definite trend to substitute cesarean section for midforceps delivery. It has been shown by Thoms[14] that even a minimal degree of midplane contraction may prove an unsurmountable obstacle for delivery of a living child. It is not always possible to prognosticate a midforceps delivery with a great degree of accuracy. We firmly believe that, whenever difficult midforceps delivery is anticipated, cesarean section is the preferred method of treatment.

Asphyxia was noted in 24 instances. These cases were divided as delayed delivery of the after-coming head in 4, prolapsed cord in 6, abruptio placentae in 13, and aspiration of foreign material in 1. Note that breech delivery accounted for 6 deaths, 4 in delay of the head and 2 in prolapse of the cord. The breech again assumes large proportions as a complication. Occult prolapse of the umbilical cord can be determined only by frequent auscultation of the fetal heart tones. Those that were salvaged owe their existence to the alertness of the labor nurse. Abruptio placentae can usually be diagnosed with accuracy. However, the severity of the separation and the attendant maternal shock frequently preclude any possibility of fetal sal-

TABLE 3. CAUSES OF DEATH IN 70 NEO-NATAL DEATHS AMONG 3751 INFANTS

Factor	*Group One*	*Group Two*	*Group Three*	*Group Four*	*Total*
Atelectasis	3	0	1	0	4
Birth trauma	3	0	1	14	18
Malformations	2	2	1	12	17
Asphyxia (aspiration)	0	1	0	0	1
Asphyxia (delayed breech)	0	1	0	0	1
Asphyxia (abruptio)	4	0	0	2	6
Hemorrhagic disease	0	1	0	0	1
Adrenal hemorrhage	0	0	0	2	2
Erythroblastosis	0	0	0	6	6
Pneumonia	1	0	1	3	5
Prematurity	3	0	0	0	3
Unknown	1	0	0	5	6

vage. We believe that a clear, concise policy for handling this complication should be formed on all obstetrical services.

Atelectasis accounted for 11 fetal deaths. This is, to many, an unsatisfactory diagnosis and is felt to be a sign of complication rather than a primary cause[1]. Several items are of note. In the case of 1 premature infant, the mother was given 15 mg. of morphine sulfate just 1 hour and 10 minutes prior to delivery. The alleged reason was to halt premature labor. One cannot help feeling that the infant's respiratory center was so depressed that it would not respond. Again, a premature infant was delivered after a rapid labor without an episiotomy. We feel that this infant's sensorium was so depressed on a mechanical basis that it, too, was unable to respond. In another instance, a term infant was delivered as a breech, with delivery noted as "easy". For this case we still need a reason. The hyaline membrane reported by Potter[4] was noted in 3 instances. In 2, the infants were delivered by section. The indications were placenta praevia and repeat section. The normal stimulus to respiration noted in vaginal delivery is certainly absent following this operation. This fact has been noted by many observers[11,12]. The infant in the placenta praevia case may well have been in dire oxygen deficit from maternal anemia. This could initiate respiratory movements *in utero*, with subsequent aspiration of amniotic fluid. Development of the hyaline membrane has not been noted as frequently in this series as in others. In another infant, a twin was not recognized. Pitocin was given to facilitate delivery of the placenta, and most certainly caused anoxic brain damage.

Toxemia of pregnancy was the probable cause of death in 7 stillbirths. It is well known that the longer a severe albuminuria exists, the greater are the chances for a damaged baby. We believe that in a toxemia that does not respond to treatment in 24 to 48 hours, the pregnancy should be terminated in the most appropriate fashion. Labor is induced if the cervix is ripe; section is performed if the cervix is long and closed. This policy, or good fortune, may account for the relatively small number of toxemic deaths in this survey.

Thirteen cases must be classified as cause unknown. Autopsies were obtained in only a few. In 3 cases in which postmortem examination was performed, the pathologist's report was "no evidence of any disease process". In the remaining ones we also have no answer. Three infants were alive when crowning and were delivered easily, but were born dead. The shock of delivery may have been the etiological agent. In the others, no cause can be advanced for the fetal loss.

Erythroblastosis fetalis accounted for the loss of 9 infants, all mature. Hemorrhagic disease of the newborn was the factor in one premature. At the present writing, treatment of the sensitized mother and her infant is not definite. Numerous methods of treatment have been suggested, but all have been severely criticized. Perhaps, in the near future, the status of cesarean section and exchange transfusion will be crystallized.

Maternal syphilis caused 4 stillbirths. As the over-all incidence of venereal disease has fallen, the fetal loss from this infection has decreased. In all 4 cases, treatment was inadequate. All the luetic stillbirths occurred in Negroes who first reported to their physicians late in pregnancy.

Intra-partum infection was responsible for 2 deaths. In one there was a high fever for 3 days, which has a

known deleterious effect on the fetus[5]. In the other, the amniotic sac was ruptured 3 days prior to admission. The fluid was greenish and very malodorous. Both women were adequately treated with antibiotics.

Pneumonia was the cause of death in 5 instances. In 2 cases, one premature and one mature, the membranes were ruptured for 24 hours before the onset of labor. Neither mother had received prophylactic penicillin. In the remaining 3, cerebral injury was included in the clinical impression. Autopsy disclosed only bronchopneumonia. All the infants were vigorously treated with appropriate antibiotics.

Bilateral adrenal hemorrhage was noted twice. It occurred in full-term infants following deliveries noted as easy and uncomplicated. At present, no reason can be adduced as to the etiology of this factor.

Prematurity alone was noted as the diagnosis in only 3 cases. All were in Group 1. No obstetrical or maternal complications were noted in any of the 3.

Maternal factors in fetal salvage were noted as the cause of fetal loss in 22 cases. They were erythroblastosis, toxemias of pregnancy, syphilis, and intra-partum infection. This, then, accounts for 16.4% of infants that failed to survive. Obstetrical factors were present in 44 (32.8%). They were trauma of labor and delivery, abruption of the normally implanted placenta, prolapse of the cord, and delay of delivery of the after-coming head. If the malformations incompatible with life are excluded, the figures are altered perceptibly. Then, in the premature infants, obstetrical factors account for 34% of the deaths and maternal factors for 9%. In the mature infants, obstetrical factors account for 46% of the deaths and maternal factors for 28.5%. The mortality for breech delivery was 8.5% in the mature infants. In the prematures, breech delivery mortality was 11.1%.

Summary. 1. This study concerns 52 premature and 82 mature infants that failed to survive in a series of 3751 deliveries. Of this group, congenital anomalies incompatible with life were the designated cause of death in 24.6%.

2. The corrected fetal mortality, excluding malformations, is 1.8% of all mature infants. For the prematures of all 3 groups, the corrected mortality is 15.3%

3. In premature infants, 43% have obstetrical or maternal complications which definitely influence adversely their chance to survive. In mature infants, these factors were present in 74.5%.

4. Autopsy percentage in this series was 64%.

Conclusions. 1. Breech delivery presents the greatest hazard to both mature and premature infants.

2. Better psychological preparation for the onset of labor, as practiced in various clinics, will decrease the need for sedation. A normal infant is the goal, not an amnesic and well-anesthetized mother.

TABLE 4.—TOTAL FETAL SALVAGE

Group	*Total*	*Stillborn*	*Neo-natal*	*Number Living*	*Survival Percentage*
1	38	10	17	11	28.9
2	49	10	5	34	69.3
3	180	6	4	170	94.4
4	3484	38	44	3402	97.7

3. Irrespective of the birth weight of premature infants, a child born without the handicap of obstetrical complication or a sick mother has an excellent chance to survive.

4. While our neonatal mortality rates compare favorably with those of most other hospitals, we feel that we are only well started on the road to irreducible mortality.

REFERENCES

1. **Beck, A. C.**: Am. J. Obst. and Gynec., **51**, 173, 1946.
2. **Breose, B. B., Jr.**: J. Pediat., **12**, 648, 1938.
3. **Dana, E. S.**: Am. J. Obst. and Gynec., **51**, 329, 1946.
4. **Davis, M. E.**, and **Potter, E. L.**: J. Am. Med. Assn., **131**, 1194, 1946.
5. **DeLee, J. B.**: The Principles and Practices of Obstetrics, 7th ed., Philadelphia: W. B. Saunders Company, 1938.
6. **Dipple, A. L., Johnson, H. W.**, and **Cornelius, J. L.**: Am. J. Obst. and Gynec., **54**, 1004, 1947.
7. **Dunham, E. C., and McAlenny, P. F., Jr.**: J. Pediat., **9**, 717, 1936.
8. **Fox, M. D., Krumbiegel, E. R.**, and **Teresi, J. L.**: Lancet, **1**, 746, 1948.
9. **Haas, R. L.**: Am. J. Obst. and Gynec., **50**, 406, 1945.
10. **Koch, L. A., Weymuller, C. A.**, and **James, E.**: J. Am. Med. Assn., **136**, 217, 1948.
11. **Lamb, T. M.**: Brooklyn Hosp. J., **7**, 4, 1949.
12. **Morison, J. E.**: J. Obst. and Gynaec., Brit. Emp., **56**, 393, 1949.
13. **Taylor, E. S., Phelen, J. R.**, and **Dyer, H. L.**: J. Am. Med. Assn., **141**, 904, 1949.
14. **Thoms, H.**, and **Wyatt, R. H.**: Am. J. Obst. and Gynec., **59**, 424, 1950.
15. **Tyson, R. M.**: J. Pediat., **28**, 648, 1946.

A DIAGNOSTIC PULMONARY ARTERY PULSE PRESSURE CONTOUR IN PATENT DUCTUS ARTERIOSUS FOUND DURING CARDIAC CATHETERIZATION

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Various reports of cardiac catheterization studies in patent ductus arteriosus have appeared in the literature[1-5]. In all these the diagnosis during catheterization was established by a significant rise in oxygen content between the right ventricle and main pulmonary artery. Pressure studies in the right ventricle and pulmonary artery have received little attention. Dexter and associates[2] mentioned that of 7 patients with patent ductus arteriosus studied, some had pulmonary hypertension, but that the majority had normal pulmonary artery pressures. The purpose of this report is to describe a characteristic and diagnostic pulse pressure contour found in the pulmonary artery during cardiac catheterization of patients with patent ductus arteriosus.

The following 2 cases have been chosen to illustrate this finding:

Case Reports. Case 1. An 18-year old colored female had been in good health until a continuous heart murmur was discovered during a recent pregnancy. The diagnosis of patent ductus arteriosus was made and it was decided to perform cardiac catheterization prior to surgical correction of the abnormality.

The blood pressure was 120 mm. of mercury systolic, 50 diastolic. The heart was not enlarged. At the pulmonic area a systolic thrill was present and a continuous "machinery-like" murmur was heard. The electrocardiogram was normal. Fluoroscopic examination showed a normal-sized heart with no abnormality of the pulmonary vascular tree.

The results of cardiac catheterization are given in Table 1. There was a significant rise in oxygen content of 2 volumes per 100 cc. when passing from the right ventricle to the pulmonary artery. The right ventricular systolic pressure was elevated, and in the pulmonary artery both systolic and diastolic pressures were moderately elevated. A continuous pressure record (Fig. 1) was taken while the catheter was slowly withdrawn from the right pulmonary artery to the main pul-

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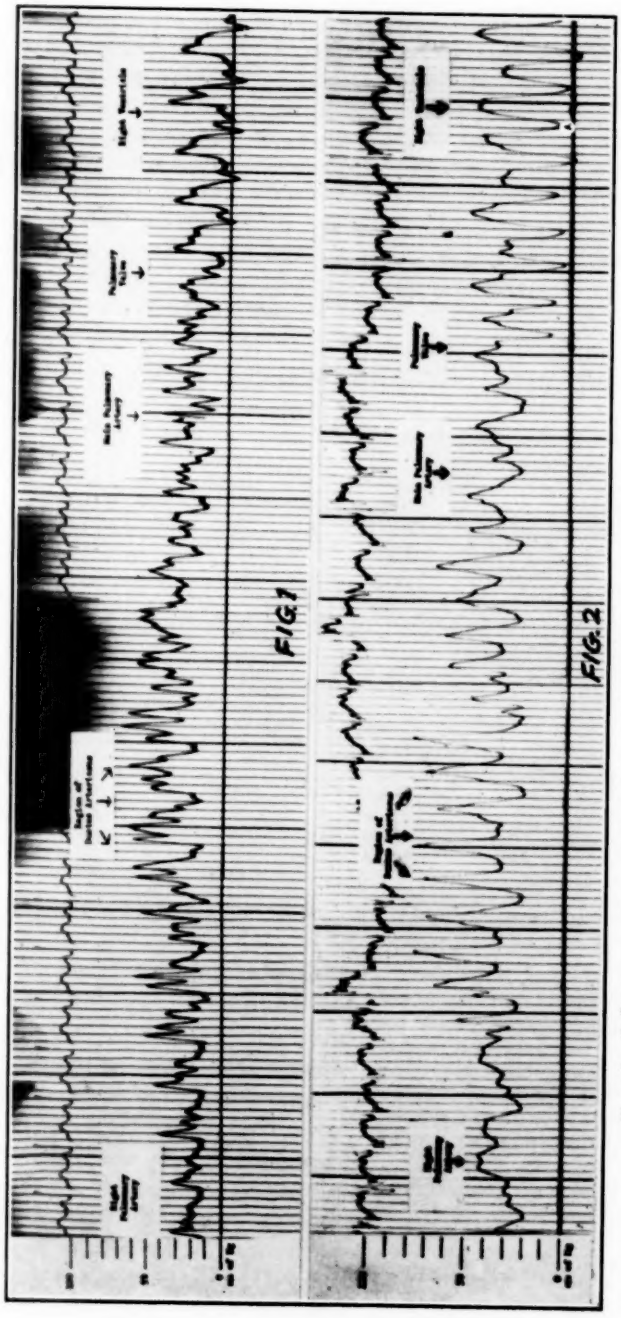

FIG. 1.—Pulmonary artery and right ventricular pressure study in a case of patent ductus arteriosus (V. K., P. F. 1044-727).

FIG. 2.—Pulmonary artery and right ventricular pressure study in a case of patent ductus arteriosus (D. H., P. F. 1203-098).

monary artery and finally into the right ventricle. From Fig. 1 it can readily be seen that there is an abrupt rise in both systolic and diastolic pressures at the site of the patent ductus arteriosus. The pulmonary artery pressures proximal and distal to the ductus were found to be about the same. At operation a patent ductus arteriosus, about 8 to 10 mm. in diameter and 1 cm. in length, was found. The ductus was obliterated by means of multiple transfixion sutures and ligatures.

monary arteries were enlarged and had expansile pulsations.

The results of cardiac catheterization are given in Table 2. There was a significant rise in oxygen content of 2 volumes per 100 cc. when passing from the right ventricle to the pulmonary artery. Pressures were elevated in both the right ventricule and the pulmonary arteries. Fig. 2 is a continuous pressure record taken while the catheter was slowly withdrawn from the right pulmonary artery into the right

TABLE 1.—RESULTS OF CARDIAC CATHETERIZATION IN CASE 1 (V. K., P. F. 1044-747)

Station	*Pressure* (*mm. of Hg.*)	*Oxygen Content* (*vol. per 100 cc.*)	*% Oxygen Saturation*
Superior Vena Cava	5/2	11.2	71.0
Right Atrium	5/2	10.8	68.9
Right Ventricle	50/0	11.1	71.0
Main Pulmonary Artery	50/14	13.1	83.3
Right Pulmonary Artery	35/13	12.9	83.2
Peripheral Right Pulmonary Artery	18/5	15.0	95.5

Oxygen Capacity: 15.7 vol. per 100 cc. = 100% Saturation.

TABLE 2.—RESULTS OF CARDIAC CATHETERIZATION IN CASE 2 (D. H., P. F. 1203-098)

Station	*Pressure* (*mm. of Hg.*)	*Oxygen content* (*vol. per 100 cc.*)	*% Oxygen Saturation*
Superior Vena Cava	0/2	7.0	62.5
Right Atrium	0/2	6.8	60.8
Right Ventricle	45/0	7.7	68.2
Main Pulmonary Artery	45/20	9.8	86.8
Right Pulmonary Artery	40/20		
Left Femoral Artery		11.4	99.0

Oxygen Capacity: 11.6 vol. per 100 cc. = 100% Saturation.

CASE 2. A 2-year old female colored infant was admitted to the hospital on March 25, 1950, because of an infection of the upper respiratory tract. On admission a continuous heart murmur was discovered which was thought to be characteristic of a patent ductus arteriosus. The patient was referred for cardiac catheterization prior to surgical correction of the abnormality.

The blood pressure was 85 mm. of mercury systolic, 40 mm. diastolic. There was Grade 2 cardiac enlargement. At the pulmonic area both a prominent systolic thrill and a continuous "machinery-like" murmur were present. The electrocardiogram was normal. Fluoroscopic examination showed Grade 2 generalized cardiac enlargement. The pulventricle. Similar to Case 1, there was an abrupt rise in both systolic and diastolic pressures at the site of the ductus. The pressure increase was accompanied by a marked change in pulse contour.

Summary. A characteristic pulse pressure contour in the pulmonary artery in patent ductus arteriosus has been described. This is best demonstrated by a continuous pressure recording while the catheter is slowly withdrawn from the right pulmonary

artery into the right ventricle. It is believed that this specific local elevation of systolic and diastolic pressure represents the transmission of systemic pressure through the patent ductus itself.

REFERENCES

1. **Cournand, A., Baldwin, J. S.,** and **Himmelstein, A.:** Cardiac Catheterization in Congenital Heart Disease. New York, The Commonwealth Fund, 1949.

2. **Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C.,** and **Evans, J. M.:** J. Clin. Invest., **26**, 561, 1947.

3. **DuShane, J. W.,** and **Montgomery, G. E.:** Proc. Staff Meet. Mayo Clin., **23**, 505, 1948.

4. **Taylor, B. E., Pollock, A. A., Burchell, H. B., Clagett, O. T.,** and **Wood, E. H.:** Am. J. Physiol., **155**, 472, 1948.

5. **Zimdahl, W. T.,** and **Chapman, D. W.:** Ann. of Int. Med., **32**, 489, 1950.

INADEQUACY OF THE GLYCEMIC REACTION TO EPINEPHRINE AS A MEASURE OF HEPATIC GLYCOGEN

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Many attempts have been made to measure the carbohydrate reserve in man. Rise in blood sugar level after the injection of epinephrine was suggested as a measure of hepatic glycogen some time ago, but marked variability in results obtained led to abandonment of the test until the recent work of Kinsell *et al.*[8] in standardizing the method eliminated some of the difficulties encountered by earlier authors. However, the use of Kinsell's procedure here over a period of 12 months revealed additional sources of error.

Material and Methods. Observations were made during the period from Oct. 20, 1949, to Oct. 18, 1950. Seventy-four patients, ranging in age from 16 to 50 years, were studied a day or two after admission to the hospital for treatment of severe neurosis or of psychosis. The procedure used was that of Kinsell *et al.*[8] except that the preparatory period of forced feeding of carbohydrate was omitted; blood sugar concentration was estimated by means of the method of Folin and Wu[6]. In 5 instances the test was repeated after 3 days during which the patients were given 300 gm. daily of carbohydrate besides that provided by the regular hospital diet. In addition, in 39 cases, eosinophil counts were made, as described previously[1], before and again 4 hours after the injection of epinephrine. The epinephrine was given intramuscularly in amounts equal to 0.01 mg. per kg. of body weight.

Observations. The rise in blood sugar after the injection of epinephrine was variable. The average increase varied with the time of year (Table 1) and was between 50 and 62 mg./100 cc. from October to May, inclusive, and between 29 and 38 mg./100 cc. from June to September, inclusive. Averaged by 4-month periods, the values were 32 mg./100 cc. for the summer, 59 mg./100 cc. for the fall–winter period, and 57 mg./100 cc. for the winter–spring months.

When the increase in blood sugar in the first hour after injection of epinephrine was compared with fall in blood eosinophilic cells 4 hours after injection of the drug, it was apparent that the 2 values varied in parallel fashion, if allowance was made for the time of the year at which the tests were carried out (Fig. 1).

After feeding of large amounts of carbohydrate for 3 days and repetition of the test a day later, there was a decrease in glycemic response in the second test in all 5 subjects so studied (Table 2).

Discussion. Variations in the glycemic response to epinephrine with time of year encountered in the present study are probably not owing to the use of patients in different categories as subjects at different times. The relative admission rates to the hospital of the different categories were not influenced by season and, moreover, it has been

TABLE 1.—AVERAGE RISE IN BLOOD SUGAR LEVEL AFTER EPINEPHRINE 0.01 MG./KG.

Month	*Monthly Number*	*Average Rise*	*2-Month Number*	*Average Rise*	*4-Month Number*	*Average Rise*
June	5	29				
July	7	32	12	31	21	32
Aug.	6	32				
Sept.	3	38	9	33		
Oct.	5	50				
Nov.	7	59	12	56	29	58
Dec.	4	53				
Jan.	13	62	17	60		
Feb.	2	55				
March	5	58	7	57	24	57
April	8	51				
May	9	61	17	56		

TABLE 2.—RESULTS INJECTING EPINEPHRINE 4 DAYS APART

	First Test	*Second Test*
Case F	40 mg./100 cc.	11 mg./100 cc.
M	48 "	34 "
B	67 "	54 "
E	82 "	30 "
W	63 "	44 "
Averages	60 "	35 "

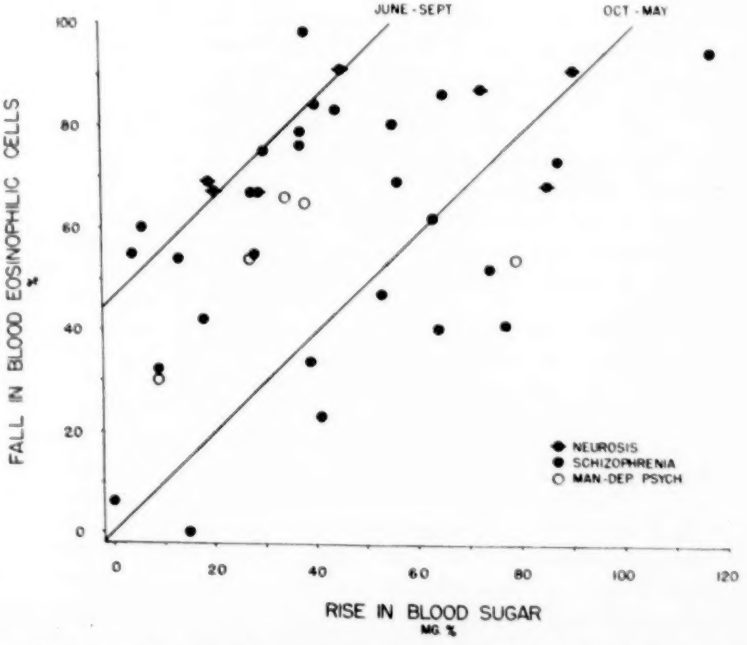

FIG. 1.—Relation between decrease in eosinophils and rise in blood sugar level after injection of epinephrine.

shown that the distribution of values obtained in the test is not markedly different for the various categories[2]. Seasonal variation in hepatic glycogen content has been described in various mammalian species; this material has been reviewed extensively by Swensson[12]. Although this phenomenon has not been reported in man, the data of the present study suggest that it may occur, at least under the climatic conditions found in New England.

The finding that some patients with mental disorders show less than expected amounts of change in blood sugar level and eosinophilic count after epinephrine is of interest. Rise in blood sugar level and the fall in eosinophilic count after injection of epinephrine involve different physiological processes, and the fact that both show parallel variations suggests that a mechanism which inactivates the injected epinephrine operates to a variable degree in the patients studied. Inactivation of epinephrine in the body is not understood[9,13,14], but it does appear to occur in the peripheral tissues rather than the viscera or the blood. This mechanism may result in false low results in the epinephrine test for hepatic glycogen in some patients with mental disorders. It is of interest in this connection that injury to the brain in man has the same effect on the glycemic response to epinephrine[11].

Repeated injection of epinephrine results in diminution in cardiovascular reaction to it in man and in animals[3,10,11]. The present study shows that injection of epinephrine also diminishes the glycemic response in subsequent tests; a second test done 4 days after the first always yielded lower values in spite of the fact that the subjects so studied had had anorexia before admission and had been given excessive amounts of carbohydrate in the interval between the 2 tests. These observations corroborate the earlier findings of Freeman *et al.*[7]. Whether the diminished responsiveness seen in some patients with mental disease when first studied is a consequence of previous repeated overproduction of epinephrine during paroxysms of rage or fear cannot be stated.

The present study shows that two factors may cause difficulty in the interpretation of the epinephrine glycemic test for hepatic glycogen. These are a) seasonal variations in results probably indicative of seasonal variations in the glycogen content of the liver, and b) diminished reactivity apparently as a result of abnormally great inactivation of epinephrine. The latter may be seen on the occasion of the first test in some patients with mental disease, and is produced in others by repetition of the test. Whether additional sources of error may exist cannot be stated; however, the work of de Bodo *et al.*[4,5] in dogs suggests that adrenal insufficiency also may result in false low values. At any rate, the difficulties discussed here are sufficient in themselves to impair the value of the test as a measure of hepatic glycogen.

Summary and Conclusions. Effects of intramuscular injection of epinephrine in doses of 0.01 mg./kg. of body weight on the blood sugar level were studied in 74 patients with mental disorders during the course of a year. Seasonal variation in the glycemic response was observed, the average increase in blood sugar level from June to September being approximately half of that found from October to May. In addition, some of the patients exhibited unusually small glycemic responses, interpreted as owing probably to inactivation of the injected epinephrine; this phenomenon occurred in some patients when first studied and was produced in five others by repeated injection of the drug. These considerations impair the validity of the test as a measure of the amount of hepatic glycogen in man.

REFERENCES

1. **Altschule, M. D., Parkhurst, B. H.,** and **Tillotson, K. J.**: J. Clin. Endocrinol., **9,** 440, 1949.

2. **Altschule, M. D., Promisel, E.,** and **Mora-Castaneda, F.**: Arch. Neurol. & Psychiat. In Press.

3. **Cameron, D. E.**: Am. J. Med. Sci., **210,** 281, 1945.

4. **de Bodo, R. C., Slater, I. H., Weisberg, H. F.** and **Prescott, K. F.**: Fed. Proc., **7,** 26, 1948.

5. **de Bodo, R. C., Kiang, S. P.,** and **Slater, I. H.**: Ibid., **8,** 32, 1949.

6. **Folin, O., Wu, C., Peters, J. P.,** and **Van Slyke, D. D.**: Quantitative Clinical Chemistry, Vol. II. Methods. Baltimore, Williams and Wilkins Co., 1932, p. 456.

7. **Freeman, H., Looney, J. M., Hoskins, R. G.,** and **Dyer, C. G.**: Arch. Neurol. & Psychiat., **49,** 195, 1943.

8. **Kinsell, L. W., Michaels, G. D., Weiss, H. A.,** and **Barton, J. C., Jr.**: Am. J. Med. Sci., **217,** 554, 1949.

9. **Markowitz, J.,** and **Mann., F. C.**: Am. J. Physiol., **89,** 176, 1929.

10. **Parkins, W. M., Swingle, W. W., Taylor, A. R.,** and **Hays, H. W.**: Am. J. Physiol., **123,** 668, 1938.

11. **Ruesch, J.,** and **Bowman, K. M.**: J. Nerv. & Ment. Dis. **99,** 842, 1944.

12. **Swensson, A.**: Acta physiol. Scandinav., Suppl., **33,** 1945.

13. **Vigran, I. M.,** and **Essex, H. E.**: Am. J. Physiol., **162,** 230, 1950.

14. **Weinstein, S. S.,** and **Manning, R. J.**: Science, **86,** 19, 1937.

RETROGRADE EXTRUSION OR PROLAPSE OF THE GASTRIC MUCOSA INTO THE ESOPHAGUS

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Retrograde extrusion, prolapse, or herniation of the gastric mucosa into the lumen of the esophagus is an apparently rare abnormality. Our particular interest in this problem was stimulated by the experiences with 2 patients in whom it was possible to make a detailed study of this condition.

The incidence has not been established. An exhaustive survey of the literature revealed but one case reported by Wells[2] in 1947. It appears that nothing had been written on this subject until then, and that Wells's case is the first and only description of retrograde prolapse of the gastric mucosa into the esophagus to be found in the available literature. It must be emphasized here, however, that retrograde extrusion of the gastric mucosa has no doubt been overlooked or misdiagnosed. Nothwithstanding the lack of reports of this condition, its incidence must probably be relatively higher than one would suspect. The recognition of retrograde prolapse of the gastric mucosa might be confused with the picture of herniation of the stomach through the esophageal opening of the diaphragm and this might account for the paucity of literature on the subject.

In an attempt to determine how often retrograde prolapse or extrusion of the gastric mucosa into the esophagus occurs, a study was made of 1000 adult autopsies.* In not a single instance was this condition observed. However, one might not expect to find the condition at autopsy, since the extruded mucosa tends to slide back into the stomach. The condition is more likely to be observed during an esophagoscopic or roentgenologic examination.

As far as can be ascertained there are no autopsy or surgical case reports mentioned in the literature. In available textbooks, the subject of retrograde prolapse of the gastric mucosa into the esophagus is not given recognition. This writer[1] mentions the condition in his book. It is, therefore, the purpose of this communication to present more complete clinical and roentgenologic data on the subject.

In the light of our present knowledge and experience with the forward propulsive type of prolapse of the gastric mucosa which extrudes into the pylorus toward the duodenal bulb, one might explore the possibility of considering the occurrence of a retrograde type of prolapse in which the gastric mucosa extrudes into the lumen of the esophagus.

In this presentation 2 cases are described with the Roentgen portrayal of a retrograde prolapse of the gastric mucosa into the lumen of the esophagus. It is also pointed out that this condition is a clinical entity productive of symptoms.

Case Reports: Case 1. A woman, aged 60, complained of epigastric distress, heart-

* These data were obtained from the autopsy records of the Sinai Hospital through the courtesy of Dr. Tobias Weinberg, Director of Laboratories.

burn, sour regurgitation, nausea and vomiting. Her sumptoms became worse after eating and especially on lying down. Her appetite was good. Eight years ago she had had a cholecystectomy without obtaining relief from her gastrointestinal symptoms. She still complained of recurrent intermittent pain in the upper abdomen which radiated to the back. Gastric analysis gave normal findings. A gastrointestinal examination showed a reflux of barium into the esophagus due to esophago-gastric relaxation. A sliding knuckle of gastric mucosa could be seen extruding up into the lumen of the lower esophagus, accompanying the reflux of barium (Fig. 1). This was only observed in the examination made in the prone position. There was evidence of an intermittent retroperistalsis which was accentuated during the act of regurgitation or vomiting. The roentgenogram showed the prolapsed mottled gastric mucosa in the region of the lower esophagus.

FIG. 1.—Case 1. Roentgenogram demonstrating the knuckle of gastric mucosa protruding into the esophagus. The folds of mucosa are shown extending above the diaphragm. A small amount of barium is seen within the lumen of the lower esophagus. Note the simulation of a hernia of the stomach through the esophageal opening.

CASE 2. A woman, aged 49, complained intermittently for a few years of a lump in her throat, nausea, vomiting, discomfort after eating, and epigastric pressure. There was no actual pain. Her appetite was fair. A gallbladder Roentgen examination revealed a normally functioning gallbladder without stones. A gastrointestinal Roentgen study, with the exception of the changes noted in the lower esophagus, was negative. Fluoroscopic examination of the esophagus showed the barium meal to descend readily when in the erect position and to be completely emptied before the roentgenograms were made. Under fluoroscopic examination in the prone—oblique position, a small mottled protrusion was seen to rise up into the lumen of the lower esophagus (Fig. 2). The lumen of the esophagus was partly outlined by some reflux of barium. The extruded shadow of gastric mucosa disappeared when the patient was placed in the erect position. From the fluoroscopic study it seemed clear that the prolapse of gastric mucosa behaved like a ball

and valve; this was especially noted when the patient became nauseated and attempted to vomit; this action was accompanied by a reverse peristalsis of the stomach.

Discussion. ETIOLOGY. Since there has been little if any clinical study of the retrograde type of extrusion of the gastric mucosa, its etiology has received insufficient attention. A number of anatomic–physiologic factors might provoke the initial changes resulting in a retrograde prolapse. One or more of the following factors may be responsible for this condition: 1) relaxation of the esophago-gastric opening, 2) excessive redundancy of the gastric mucosa, 3) retrograde peristalsis of the stomach, and 4) repeated regurgitation and excessive or violent vomiting. This condition is probably more common in women who have borne children, especially in those who have had excessive and prolonged vomiting during pregnancy. It may also occur in the aged due to degenerative changes causing relaxation of the esophago-gastric opening.

Although surgical and pathologic proof of the presence of this condition is lacking at this time, we believe that the Roentgen and esophagoscopic findings are sufficiently definite to permit the conclusion that retrograde extrusion of the gastric mucosa into the esophagus is a clinical entity. Experimentally, it can be shown in the fresh autopsy specimen of the stomach that the gastric mucosa can readily be brought up into the lumen of the esophagus. The gastric mucosa of the stomach is normally loosely attached to the submucosa, although this is less marked along the lesser curvature of the cardia. The gastric mucosa may be considered as normally somewhat redundant; however, under certain abnormal conditions the redundancy of the gastric mucosa becomes more

FIG. 2.—Case 2. Roentgenogram of a small mottled mucosal mass in the lower esophagus. A small amount of barium is seen in the lower esophagus. Note the simulation of a hernia of the stomach through the esophageal opening.

marked and the folds elongate and enlarge. In the presence of reversed peristalsis this abnormal redundant gastric mucosa may prolapse into the lumen of the esophagus. The extruded gastric mucosa is further involved by becoming congested, hypertrophied, and inflamed. It may be the cause of bleeding as a result of erosion, ulceration, or congestion.

Abnormal physiologic changes of the stomach are commonly observed. There are many pathologic–physiologic phenomena which may cause retrograde peristalsis. These conditions are usually associated with excessive vomiting.

Symptoms. The recognition of the nature and effect of retrograde prolapse of the gastric mucosa into the lumen of the esophagus as a causative factor in the production of clinical manifestations has been given litle consideration. Recent studies of prolapse of the gastric mucosa involving the pyloroduodenal outlet have focused attention on the role this condition plays in the production of clinical symptoms. Increasing clinical experience has brought to light many obscure cases which previously passed unnoticed or were diagnosed incorrectly. In the retrograde esophageal prolapse, the symptoms are more likely to be gastric rather than esophageal, but when the esophagus is obstructed the symptoms are chiefly esophageal. The symptoms are variable and at times may be few or absent. It is important to emphasize that the symptoms are often provoked when the patient is lying down, accounting for the frequence of nocturnal symptoms, whereas in the erect position he may be free of trouble.

Dysphagia, regurgitation, nausea, vomiting, and substernal and epigastric distress are the symptoms oftenest encountered. There may be bleeding, either occult or visible blood, due to erosion, ulceration, and congestion. The condition could conceivably cause symptoms of esophageal obstruction, either intermittent or persistent. There can be episodes of acute or subacute pain as a result of pinching off of the gastric mucosa in the esophagus by spastic contracture or stricture. The symptoms most often simulate those encountered in hernia of the stomach through the esophageal opening of the diaphragm. However, nausea, vomiting, and regurgitation are invariably observed in retrograde prolapse of the gastric mucosa into the esophagus and are more or less characteristic of the latter condition.

Diagnosis. Retrograde prolapse of the gastric mucosa is a roentgenologic entity. It cannot be diagnosed with any degree of accuracy by any other means, with the possible exception of the esophagoscope. The Roentgen method of examination is the means of choice in recognizing this condition. Furthermore, the Roentgen examination affords the one sure means of yielding information that may not be otherwise obtained. Conclusive and indisputable evidence may be adduced by this examination to substantiate the diagnosis of retrograde extrusion of the gastric mucosa.

However, it must be pointed out that unless the condition is especially searched for, it may elude recognition. Retrograde prolapse can be clearly demonstrated by fluoroscopy in the prone, prone–oblique, and Trendelenburg positions. During this examination the reflux of barium and the protrusion of the gastric mucosa can be seen to slide together, back and forth in the lumen of the esophagus. The lower end of the esophagus is often outlined by barium and the mass of the extruded redundant gastric mucosa must be carefully observed to slide into the lumen. This observation is a diagnostic clue which must be stressed, since one must make certain that the condition is not a hernia through the esophageal open-

ing of the diaphragm. The condition is not observed in the erect position unless the herniated gastric mucosa is caught within the esophagus. The retrograde prolapse or extrusion of the gastric mucosa is best observed during and following an episode of regurgitation or vomiting.

The normal mucosal pattern of the lower esophagus shows the folds arranged longitudinally. They are usually low and superficial, and therefore are overshadowed by the prolapsed gastric mucosa. An irregular mottled protrusion of the gastric mucosa can be seen to extend up from the stomach into the lumen of the esophagus. The esophagus may also fill with barium at the same time due to the esophago-gastric relaxation. Ordinarily only a small knuckle of gastric mucosa is extruded (Fig. 3). It usually protrudes into the esophagus for a few centimeters, but rarely may extend upward for some distance. The retrograde prolapse of gastric mucosa is usually intermittent. It is nearly always associated with relaxation of the cardio-esophageal opening with some widening of the lumen or a bulbous appearance of the lower esophagus. The extruded gastric mucosa is shown as a mottled mushroom mass, of irregular surface, producing a filling defect in the lower esophagus (Fig. 4). Occasionally there may also be some narrowing of the cardia of the stomach and displacement or obliteration of the gas bubble due to the invagination of the mucosa. When the condition is marked, there may be puckering or cascading of the gastric contour as a result of the tugging effect of the retrograde prolapse. The condition is commonly associated with retroperistalsis of the stomach, hypertrophic gastritis, and esophagitis.

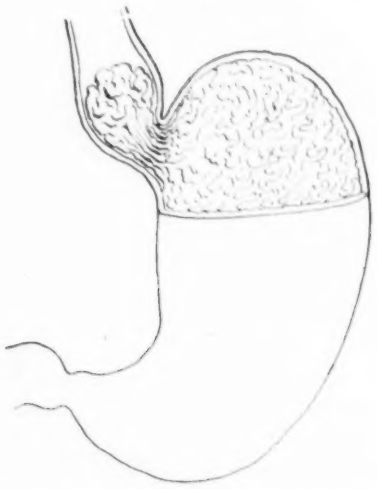

FIG. 3.—Drawing illustrating the retrograde extrusion of the gastric mucosa into the lumen of the esophagus.

The following Roentgen findings may be observed in retrograde extrusion of the gastric mucosa: 1) shadow of the prolapsed mucosa, shown as a mottled filling defect in the lower esophagus; 2) intermittent retardation of the descent of barium in the lower esophagus; 3) crescent-shaped pressure filling defect at the head of the barium column; 4) obstructive signs when

complicated by spasm or stricture; 5) lumen of the esophageal wall intact and regular, without intrinsic defect; 6) mushroom filling defect or a shelving defect in the column of barium where it meets with the extruded gastric mucosa (Fig. 4); 7) retrograde gastric peristalsis; 8) reflux of barium into the esophagus due to cardio-esophageal relaxation; 9) dilatation or bulbar appearance of lower esophagus; 10) ball-valve effect of the extruded gastric mucosa; 11) narrowing of the cardia or fundus of the stomach; and 12) puckered or kinked defect in gastric contour due to tugging of the prolapsed mucosa in extreme cases.

The extrusion of the gastric mucosa is recognizable in the esophagoscopic examination. A polypoid mass is seen protruding into the lumen of the lower esophagus. The condition may not always be demonstrated by this procedure, since the esophagoscope may push the prolapsed gastric mucosa down into the stomach. This may account for its apparent rarity, since, according to Zinn[3], in approximately 2000 esophagoscopic examinations not a single instance of retrograde herniation or extrusion of the gastric mucosa into the esophagus was encountered. But it is essential to perform an esophagoscopic examination in all instances in order to rule out an intrinsic lesion. In Wells's case the herniated gastric mucosa produced an obstruction in the lower esophagus and was visualized by the esophagoscopist.

FIG. 4.—Drawing illustrating the mushroom type of filling defect in the lower esophagus at the head of the column of barium as it meets the mass of retrograde gastric mucosa.

DIFFERENTIAL DIAGNOSIS. The Roentgen picture has been confused with that of hernia of the stomach through the esophageal opening of the diaphragm. In some instances, where there is a small knuckle of barium in the lower esophageal area believed to be due to a hernia, the condition could be due to a retrograde extrusion of the gastric mucosa.

In the differential diagnosis the following conditions must be considered: 1) hernia of the stomach through the esophageal opening of the diaphragm;

2) retained barium in the lower esophagus; 3) regurgitation or reflux of barium into the lower esophagus; 4) retrograde prolapse of a pedunculated gastric neoplasm; 5) polypoid neoplasm of the lower esophagus; and 6) varices. The most common condition requiring differentiation is herniation of the cardia of the stomach through the esophageal opening of the diaphragm. In this condition the herniated stomach slides up outside of the esophagus and is usually displaced mesially, and the cardia of the stomach can be seen above the diaphragm. In hernia there is no gaping or relaxed esophago-gastric opening, and reversed peristalsis and vomiting do not usually occur. Regurgitation or reflux of the gastric contents into the esophagus occurs more often in prolapse. In retrograde prolapse of the gastric mucosa the redundant mass protrudes upward into the esophageal lumen, and the entire stomach contour remains within the abdomen in its normal subdiaphragmatic position.

Summary and Conclusions. 1. Retrograde extrusion of the gastric mucosa into the lumen of the esophagus is a clinical and roentgenologic entity.

2. The incidence of retrograde extrusion of the gastric mucosa is probably greater than the meager literature suggests.

3. The condition presents a clinical picture which simulates that of hernia of the stomach through the esophageal opening, and therefore it it probably confused with such herniation.

4. The roentgenologic demonstration of retrograde prolapse of the gastric mucosa is clearly possible and its roentgenologic criteria are here described.

5. Two cases are presented, illustrating the clinical manifestations and the roentgenologic picture of the condition.

REFERENCES

1. **Feldman, M.:** Clinical Roentgenology of the Digestive Tract, 3rd ed., p. 189, Baltimore: Williams & Wilkins Co., 1948.

2. **Wells, J.:** Am. J. Roentgen. and Rad. Therap., **58**, 194, 1947.

3. **Zinn, W. F.:** Personal communication from the Bronchoscopic Clinic, Mercy Hospital, Baltimore.

THE EFFECTS OF EXPERIMENTAL ACIDOSIS ON THE DYNAMICS OF CIRCULATION

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Various explanations have been offered for the shock-like picture occurring in diabetic and uremic coma as well as that seen in cases of acidosis associated with severe emphysema. Schechter, Wiesel, and Cohn[10] attribute the shock-like picture in diabetic coma to hemoconcentration and to the decreased blood volume subsequent to loss of sodium in the urine. They state, however, that the venous blood in such cases fails to show a lowered oxygen saturation as seen in surgical shock, and feel, therefore, that a histotoxic factor must play a role in the development of the clinical picture. Atchley and his collaborators[1] demonstrated marked sodium, potassium, and chloride loss in cases of acidosis and attributed the shock-like picture to hemoconcentration. Horvath, McMichael, and Sharpey-Schafer[5] emphasized the low blood pressure and normal cardiac output present in diabetic coma and concluded that diabetic coma is associated with a marked lowering of the peripheral resistance. Kety, Schmidt *et al.*[7] estimated the blood flow through the brain in diabetic coma by the nitrous oxide method and found that the blood flow was markedly increased as a result of diminished vascular resistance, despite the lowered CO_2 tension, and thus the CO_2 content can be eliminated as the etiological factor in the vasodilatation in these cases.

Our attention was drawn to the circulatory changes noted in induced acidosis during our attempts to correct the signs of anoxia seen in the electrocardiograms of hypothermic patients and in experimental animals. Since in hypothermia the oxygen dissociation is diminished, we felt that the resulting myocardial anoxia, as well as the continued work by the myocardium against an increased peripheral resistance in cold, was the cause of the ECG changes. Acidification of the blood, which increases oxygen dissociation, corrected the ECG changes occurring in hypothermic anoxia[8]. In studying the consequences of such an experimentally produced acidosis, certain

*Work done under contract between the Surgeon General, U. S. Army, and the New York Medical College.

observations were made which seem to have direct bearing on the circulatory changes in clinical acidosis.

Methods. Six heparinized mongrel dogs of varying weights were anesthetized with intravenous pentothal sodium. The respiration of the animals was suppressed by means of curare (Intocostrin) and artificial respiration was given through an inflated tracheal cannula by a special revolving valve. The air supply was provided from a compressed air container and the set-up permitted the collection of all the exhaled air for analysis. The valve was activated by a windshield wiper motor and this permitted regulation of the depth and rate of inspiration and expiration. An attempt was made to simulate as closely as possible the respiratory conditions prevailing prior to anesthesia.

A catheter was introduced through an incision in one femoral vein and passed up to the right auricle to permit withdrawal of blood specimens from the right heart. The position of the catheter in the right auricle was checked in each experiment by necropsy. The contralateral femoral vein was used for the acid infusions as well as for determinations of venous pressure, which were made during the intervals when the acid infusions were temporarily halted. One femoral artery was connected to a Sanborn electromanometer to permit continuous recording of systolic, diastolic, and mean blood pressures. A cannula was introduced into the opposite femoral artery to permit the withdrawal of arterial blood samples.

Arterial and venous oxygen content and capacity were determined by the method of VanSlyke and Neill; the air in the cylinder and the exhaled air were analyzed according to the method of Haldane. The pH of the blood was determined in the Cambridge research pH meter according to the method described elsewhere[4] and corrected for temperature according to the formula of Rosenthal[9].

With these methods the following data were obtained in each experiment at varying pH levels: A—V difference, oxygen saturation, stroke and minute output, heart rate, mean blood pressure, venous pressure, oxygen consumption per minute, and a factor for the peripheral resistance. This factor was calculated by dividing the mean blood pressure by the cardiac output per second per kg. of body weight. The arterial and venous blood samples for the oxygen and the pH determinations were withdrawn while the exhaled air was being collected and the mean blood pressure and the venous pressure were recorded. After at least two basic determinations the intravenous infusion of 10% gluconic acid in 5 dogs and 1-N acid sodium phosphate in 1 dog was started. The infusion was begun at the rate of 60 to 100 drops per minute. When the pH of the arterial blood started to drop, as indicated by frequent pH determinations, the rate of flow was reduced to 20 to 30 drops per minute. In each animal 2 sets of complete determinations were made during acidification. Three dogs were cooled in a box filled with cracked ice after initial determinations were made at normal body temperatures. When the body temperature had dropped to 26 to 28°C., another series of determinations was made and subsequently acidification was started. A third set of data was obtained when the pH of the arterial blood was lowered by 0.3 to 0.5 pH units.

The rapid infusion of acid sodium phosphate did not produce a shift of blood electrolytes out of the normal range except for the values for phosphorus. The infusion of gluconic acid acidifies the blood and urine. Chenoweth and collaborators[2] demonstrated that gluconic acid, even when given orally, rapidly acidifies the urine. They also demonstrated that the intravenous infusion of a 10% solution of gluconic acid led to a transitory fall in blood pressure in cats and dogs. Large doses can be given without permanent damage. Humans taking daily doses of 5 to 10 gm. orally for 3 to 6 days showed no pathologic constituents in the urine. Gluconic acid is partially broken down to glucose and partially excreted in the urine as gluconic acid[11].

Results. In all animals, acidification of the blood led to a marked increase in minute output of the heart. The increase varied widely from animal to animal. Increases from 142 to 381% above the basic values were found with pH changes of approximately 0.3 pH units.

With acidification the pulse rate decreased in all animals. The proportional increase in stroke volume, therefore, was more pronounced than the in-

crease in minute volume. Increases from 160 to 454% above the basic values were found with pH changes of approximately 0.3 pH units. There was no constant relation between the degree of change in pH and the amount of increase in stroke volume.

The increased cardiac output led to a decreased A–V difference in all animals.

The systolic blood pressure was maintained initially in most animals with two exceptions, in which there was a fall in blood pressure at the beginning of acidification. With further acidification the systolic blood pressure began to fall in all animals. The diastolic blood pressure fell in all animals with the onset of shift in blood pH. In all animals the pulse pressure increased with the start of the acidification. The venous pressure, however, remained unchanged throughout the experiments except in those animals where the pH was lowered to values around 6.8 or less. In these instances, the venous pressure fell rapidly and signs of deep shock developed.

The peripheral resistance decreased immediately in all animals at the beginning of acidification. The decrease varied between 36 and 75% below the basic value. In the group of three animals in which the peripheral resistance was markedly raised by hypothermia prior to the acidification, the decrease in resistance with acidification of approximately 0.3 pH units was 51, 66, and 73%, respectively. Tables 1 and 2 give an example of the data obtained in representative animals of the normal and the hypothermic group.

Discussion. It is a well known fact in physiology that acids dilate the blood vessels, but it seems that this knowledge has not been made use of in clinical medicine. The fact that many patients with chronic glomerulonephritis lose their hypertension when they go into uremia in the absence of cardiac failure has never been explained satisfactorily. Duncan[3] states that he has never seen a patient in diabetic coma with high blood pressure. Our experiments, in which the pH was lowered to levels occurring in clinical acidosis, demonstrate that such shifts of pH are accompanied by a marked decrease in peripheral resistance. Initially, this decrease in peripheral resistance is compensated for by an increased cardiac output and particularly by an increase in the stroke volume. Finally, with increasing acidosis, the heart is no longer able to compensate for the lowered peripheral resistance, and a fall in blood pressure with a shock-like picture results. The markedly increased cardiac output, however, does not permit the venous oxygen content to fall, as it does in surgical shock, which is not associated with an increased cardiac output. One does not need, therefore, to assume specific histotoxic factors as was done by Schechter, Wiesel, and Cohn[10] to explain the high venous oxygen content in diabetic coma.

We are aware of the fact that there are differences between the experiments described and the clinical condition of uremic and diabetic acidosis. In all our experiments the pulse rate decreased with increasing acidosis, which is not noted in clinical acidosis. Ketone bodies, with their possible importance as toxic substances, were absent. Artificial respiration prevented the animals from eliminating CO_2 by hyperventilation. Nevertheless, we feel that the circulatory changes described in these experiments furnish a basis for a better explanation than has been presented so far for the shock-like picture and fall in blood pressure that are seen in severe acidosis and coma.

Clinically, the need to restore a normal pH in cases of acidosis seems

TABLE 1.—INFLUENCE OF A CHANGE IN THE pH OF THE BLOOD ON CIRCULATORY DYNAMICS IN A DOG* AT NORMAL TEMPERATURE

Corrected pH (Arterial Blood)	*Venous O_2 Content vol./ 100 cc.*	*Arterial O_2 Content vol./ 100 cc.*	*A–V Difference vol./ 100 cc.*	*Venous Sat. %*	*Arterial Sat. %*	*Corrected vol. exp. air, cc./min.*	*O_2 Consump. cc./min.*	*Cardiac output cc./min./kg.*	*Pulse Rate per. min.*	*Stroke Vol., cc.*	*Blood Pressure*	*Mean Blood Pressure*	*Total Peripheral Resistance*
7.42	11.7	18.2	6.5	62.0	96.2	1362	11.4	27.5	160	1.1	165/130	145	44.2
6.95	12.0	17.5	5.5	64.1	94.0	1226	18.7	53.0	120	2.8	105/60	80	14.9
6.73	13.2	16.0	2.8	77.4	94.0	1371	15.9	89.0	108	5.26	110/55	75	7.9

* Dog No. 109; weight, 6.4 kg.

TABLE 2.—INFLUENCE OF A CHANGE IN THE pH OF THE BLOOD ON THE CIRCULATORY DYNAMICS OF A HYPOTHERMIC DOG.*

Rectal Temp. °C.	*Corrected pH Art. Blood*	*Venous O_2 Content vol. 100 cc.*	*Arterial O_2 Content vol. 100 cc.*	*A–V Difference vol. 100 cc.*	*Venous Sat. % %*	*Arterial Sat. %*	*Corrected vol. exp. air, cc./min.*	*O_2 consump. cc./min.*	*Cardiac output cc./min./kg.*	*Pulse rate per min.*	*Stroke vol. cc.*	*Blood Pressure*	*Mean Blood Pressure*	*Total Peripheral Resistance*
38	7.52	10.9	16.5	5.6	63.4	97.0	1997	37.25	155.0	164	4.05	150/105	120	11.2
28	7.42	10.7	17.5	6.8	57.5	95.3	1166	8.74	29.9	101	1.26	140/90	108	47.6
26	7.11	14.0	16.9	2.9	82.7	100.0	1210	7.50	60.0	57	4.49	100/30	53	16.3

* Dog No. 104; weight, 4.3 kg.

to be re-emphasized by these findings. It seems that, contrary to the prevalent trend, it would be more important to correct energetically the pH changes rather than to devote all the efforts to hydrate the patient as quickly as possible. Possibly a combination of the two procedures may be most advantageous. In so doing, blood pH values rather than the CO_2 combining power should guide the therapy, since the CO_2 content may often be misleading as was shown recently by Kety[7] and Kelsey and Leinbach[6].

Summary. 1. Six dogs were infused intravenously with acid sodium phosphate or gluconic acid to produce acidosis. The blood pH was lowered by approximately 0.3 pH units each time in two steps. Minute volume, stroke volume, blood pressure, venous pressure, and peripheral resistance were determined at each pH level.

2. Acidification increases the minute volume considerably. It depresses the pulse rate. The increase in stroke volume is proportionally greater than the increase in minute volume.

3. The systolic blood pressure does not fall initially in most instances, but does fall with increasing acidification. The diastolic blood pressure as well as the mean blood pressure fall with the onset of acidosis.

4. The venous pressure remains constant until the pH is lowered to approximately 6.8, when deep shock ensues.

5. In contrast to surgical shock, the venous oxygen content in experimental acidosis is high, and we believe this is due to the increased cardiac output.

6. The peripheral resistance decreases rapidly in all animals with the onset of acidification.

7. Acidification promptly reverses the increase of peripheral resistance induced by hypothermia.

8. The clinical implications of these findings in relation to diabetic and uremic coma are discussed and certain therapeutic suggestions are made.

9. Determinations of the pH of the blood give a better insight into the clinical condition than determinations of the CO_2 combining power.

REFERENCES

1. **Atchley, D. W., Loeb, R. F., Richard, D. W., Jr., Benedict, E. M.,** and **Driscoll, M. E.:** J. Clin. Invest., **12,** 297, 1933.
2. **Chenoweth, M. B., Civin, H., Salzman, C., Cohn, M.,** and **Gold, H.:** J. Lab. & Clin. Med., **26,** 1574, 1941.
3. **Duncan, G. G.:** Diseases of Metabolism, Philadelphia, W. B. Saunders, 1947.
4. **Graig, F., Lange, K.,** and **Carson, S.:** Blood pH Determinations: A New and Accurate Clinical Method, In Press.
5. **Horvath, S., McMichael, J.,** and **Sharpey-Schafer, E. P.:** Clin. Science, **6,** 247, 1948.
6. **Kelsey, W. M.,** and **Leinbach, L. B.:** South. M. J., **42,** 1067, 1949.
7. **Kety, S. S., Polis, B. D., Nadler, C. S.,** and **Schmidt, C. F.:** J. Clin. Invest., **27,** 500, 1948.
8. **Lange, K., Weiner, D.,** and **Gold, M. M. A.:** Ann. Int. Med., **31,** 989, 1949.
9. **Rosenthal, T. B.:** J. Biol. Chem., **173,** 25, 1948.
10. **Schechter, A. E., Wiesel, B. H.,** and **Cohn, C.:** Am. J. Med. Science, **202,** 364, 1941.
11. **Stetten, M. R.** and **Stetten, DeW., Jr.:** J. Biol. Chem., **187,** 241, 1950.

TRACHEOBRONCHIAL ASPIRATION AS A BEDSIDE PROCEDURE: INDICATIONS AND LIMITATIONS

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To secure and maintain a free airway during anesthesia and throughout the postoperative period is one of the main aims of the anesthesiologist. He avails himself of all the existing means to achieve this goal. The use of endotracheal intubation and tracheobronchial aspiration through the endotracheal tube are some of these means. It is only natural that the experience and skill accumulated in the operating room should benefit medical patients as well, and that tracheobronchial aspiration today has become part of our daily armamentarium in the treatment of the sick.

Four methods of tracheobronchial aspiration are available[3]: the single catheter method as advocated in the use of postoperative atelectasis by Haight[5] and as applied in the treatment of tracheobronchial obstruction in medical patients by Cardon[2]; suction with a small catheter through a wide bore endotracheal tube as originally described by Kuehn[6]; bronchoscopy; and suction through a tracheotomy opening.

Though the main purpose of this paper is to stress the importance of tracheobronchial aspiration as a bedside procedure and to consider its indications and limitations, an attempt is made to evaluate the 4 different methods in this connection.

Tracheobronchial aspiration has been used successfully at Mount Sinai Hospital in many cases of obstructive purulent bronchitis, in accident cases, and whenever retention of tracheobronchial secretions was diagnosed.

Technique. The method used almost routinely in our department is blind insertion of a wide bore rubber "Magill" tube through the nose of the conscious or semiconscious patient into the trachea, followed immediately by suction with a small catheter through that tube. Prior to inserting the Magill tube, the nose is inspected and the nostril chosen that seems to offer the least obstruction to the passage of the tube. The nose is sprayed with 4% cocaine to achieve shrinkage of the nasal mucosa and to make the passage of the tube easier and less traumatic. If the patient is co-operative, he is asked to inhale while we continue to spray with the nebulizer to produce local anesthesia of the pharynx and glottis. A tube is chosen that fits easily into the selected nostril and can be introduced without pressure or trauma. It is well lubricated with dibucaine or some other anesthetic ointment. The successful insertion of the Magill tube into the trachea produces a convulsive cough in nearly all patients, which brings much material into the tube. Therefore, a well lubricated French soft rubber urethral catheter that passes easily through the Magill tube is connected previously to a motor-driven suction machine so that suction can be started at once. This is very important, since the Magill tube is sometimes filled to the brim with secretions by the first cough. By skillful handling of the urethral catheter, much can be achieved; when the carina is touched, even the comatose patient coughs, plugs are loosened, and secretions can be aspirated. By changing the position of the patient, the right and the left main bronchi can be reached by the catheter. The smaller bronchi cannot be reached, but the forceful coughing expels secretions into the main bronchi and into the trachea. Trendelenburg position

helps in draining out secretions that can be aspirated subsequently.

This method of suction through a Magill tube is preferred to the so-called "single catheter" method for several reasons. In the course of the procedure, severe laryngospasm may be caused. With the large-bore Magill tube in place, we can easily force enough air or oxygen into the lungs of the patient to maintain satisfactory respiratory exchange, while this is impossible if only a small catheter has been inserted. If the vocal cords close around this small catheter, the airway is completely blocked; the patient may suffocate, or if suction is continued, collapse of the lungs can result[3]. With the Magill tube in place, suction can be interrupted. Oxygen can be reapplied and breathed in through a perfect airway for several minutes before suction is started again, a very helpful procedure in the severely anoxic patient, or when the induced coughing seems an intolerable strain. With this method, plugging of the catheter with too viscid secretions does not present a problem; the catheter can be cleaned during the procedure by running water through it, while the Magill tube remains in place.

Even with the most skillful insertion of the Magill tube, most patients feel that they are subjected to a great ordeal by the process of being intubated and aspirated, but they appreciate the instant relief obtained and are as a rule very grateful. Of course, it is important to explain to the conscious patient beforehand that he will not be able to speak during the procedure, but that he will be perfectly able to breathe. The pulse of the patient has to be palpated continuously, and the patient has to be reassured.

Since the explosive cough that is elicited is part of the treatment and is, so to say, obligatory, we must, of course, be very conscious of the fact that a great stress is put on the patient's heart during the procedure. It must be remembered that the blood pressure may rise and that bleeding may be favored, important considerations in cases of cerebral vascular accidents. Severe nasal hemorrhage may be started with every type of blind intubation and add to the obstruction. Gentleness, avoidance of pressure and force, and use of surgically clean tubes are important. In patients not in complete control of their pharyngeal reflexes, vomiting caused by attempts to introduce the tube blindly may lead to aspiration of the vomitus. These patients should be placed in the head-down position and intubation under direct vision may be preferable.

Case Reports. The following case histories (Cases 1 to 7) demonstrate some of the typical indications for endotracheal aspiration. Some of these patients, as will be pointed out, had severe coronary insufficiency and myocardial damage. However, the obstruction of the upper respiratory passages made aspirations mandatory.

CASE 1 (158287). A 64-year old man, as a result of an automobile accident, sustained a compound fracture of the left tibia, a possible skull fracture, fracture of the clavicle, and several rib fractures with puncture of the pleura and massive collapse of the right lung with mediastinal shift. He was critically ill, very cyanotic, and apprehensive. His electrocardiogram showed chronic coronary insufficiency, myocardial degeneration, and intraventricular block. His temperature was 102°F., his pulse 110 and irregular. This man was intubated through the nose and aspirated daily for 11 days; he gradually filled up again after each aspiration with secretions he was unable to cough up. Complete recovery ensued.

CASE 2 (192133). An 18-year old female attempted suicide with barbiturate. She was unconscious and cyanotic; deep reflexes were absent, pupils widely dilated. There was no response to painful stimuli. Treatment consisted of massive doses of picrotoxin, amphetamine, and caffeine, with the necessary supportive measures. Maintenance of an adequate airway was difficult because of bronchial fluids. Repeated aspiration of the throat with a catheter by the interns resulted in bleeding and trauma. A Magill tube was inserted under direct vision and left in place for 20 hours to achieve continuous suction through the tube. The endotracheal tube was withdrawn when the patient started to react. There was uneventful recovery; the only after-effects were hoarseness for a few days and sore throat.

It is important to keep in mind that prolonged intubation can cause traumatic edema of the larynx (especially in children), necrosis, and granulation. The indwelling tubes should be surgically clean. In small children and infants, if frequent tracheobronchial suction is needed, tracheotomy, as advised by many experts in cases of bulbar poliomyelitis, would be more

advisable because of the readiness with which edema of the larynx occurs.

CASE 3 (199479). A 50-year old woman vomited copiously after awakening from anesthesia. Although the patient had been placed in the head-down position when she started to vomit, and although she had recovered her reflexes before vomiting, respiratory obstruction was noted and some aspiration into the trachea of the abundant thick yellow fluid was suspected. Immediate nasotracheal intubation was done in the conscious patient and a more than moderate amount of the yellow material was aspirated by catheter through the endotracheal tube. Uneventful recovery followed in a patient in whom aspiration pneumonia would have been certain without the endotracheal suction. Had this patient eaten preoperatively, so that aspiration into the trachea of solid material might have been suspected, bronchoscopy would have been the method of choice to recover the aspirated material under direct vision.

CASE 4 (158157). Cholecystectomy and appendectomy under spinal anesthesia had been performed on a 46-year old male patient with nasal and pharyngeal congestion preoperatively and a history of bronchial asthma. Massive atelectasis of the right lung occurred on the 2nd postoperative day and was verified by Roentgen ray. There was a sudden onset of dyspnea. Cyanosis and right chest lag were observed and mediastinal displacement was diagnosed. Nasotracheal intubation was easily performed, caused an explosive cough, and a large amount of thick mucous material could be aspirated. Immediate improvement and complete recovery ensued.

Most of the patients with postoperative atelectasis that needed tracheobronchial aspiration had the atelectasis on the right side.

CASE 5 (192554). This case proves that left lung atelectasis can be cured by the same method. This postpartum patient, aged 21, showed complete atelectasis of the left lower lung with typical Roentgen-ray and physical findings. Nasotracheal suction produced violent coughing; thick plugs of mucus could be aspirated, and immediate and complete recovery followed.

CASE 6 (150607). A 65-year old man developed cyanosis on the 2nd postoperative day, after extensive bowel resection under continuous spinal anesthesia. This patient asked for and got too much sedation with morphine and meperidine. On examination, signs of retention of tracheobronchial secretions were present (râles, ronchi, wheezing), and the patient was unable to cough up secretions. Nasotracheal suction produced thick mucopurulent sputum and immediate relief. Recovery was uneventful. Incidentally, the electrocardiogram of this patient showed sinus bradycardia and auricular extrasystoles.

CASE 7 (165435). This 62-year old male was admitted with a diagnosis of chronic bronchitis, bronchiectasis, acute bronchiolitis, status asthmaticus, and chronic emphysema. Electrocardiographic findings were sinus tachycardia and an abnormal pattern. Treatment with oxygen, aerosol, antibiotics, venesection, and penicillin-epinephrine inhalation had not caused any improvement over a period of several days.

When he was seen by the author, deep cyanosis and extreme dyspnea were present. The temperature was 101°F., the pulse 140. He was comatose. Nasotracheal suction with aspiration of thick pus caused instant improvement. The patient responded, became alert, the temperature dropped to 100°, but the pulse stayed at 140. One week later, the patient again became comatose and very cyanotic. Nasotracheal suction was carried out with immediate success; the patient responded and the color improved. This time, oxygen-helium inhalation under positive pressure was suggested, because of the asthmatic component in the patient's condition. There was a remarkable improvement. After a few days of inhalation of the light mixture and more tracheal aspiration, the patient recovered and remained well for 1 whole month. He was up and walking around. His physicians thought he was ready to go home; he remained in the hospital only because there he received better care. Then suddenly his respirations became labored, he had repeated emesis, was stuporous, incontinent, and died 2 days later, in spite of all efforts to save him. A diagnosis of cor pulmonale had been made, but unfortunately permission for postmortem examination was not obtained.

The following 2 cases prove that endotracheal aspiration may occasionally prove dangerous and hasten the death of the patients.

CASE 8 (198885). This moribund patient was suffering from bacteremia (*B. aerogenes*), chills, fever up to 104°, headache, and dizziness. Pupils were unequal.

At 11:10 a.m., pulse and blood pressure were unobtainable and froth was noted

around the mouth. Vasopressor drugs were injected and subsequently blood pressure and pulse seemed satisfactory. The author was called at 11:30 a.m. to perform tracheal aspiration. A nasotracheal intubation was performed easily without any trauma. The patient coughed violently, had the aspect of great anxiety and struggled against the tube. Several persons had to hold him. There was little pus aspirated. Breathing through the tube seemed slightly easier. But death followed 2 minutes later. There was no postmortem examination.

Case 9 (200381). A 30-year old woman was dying from peritonitis, following unrecognized rupture of the appendix. The author was called because a diagnosis of the patient's "drowning in her own fluids" was made. Easy atraumatic nasotracheal intubation was performed which caused a violent cough, but brought very little material into the tube. The patient's respiration ceased, no pulse could be obtained, and artificial respiration through the tube was of no avail. Postmortem examination showed generalized peritonitis and massive emboli in the lungs. There was slight atelectasis in the lower lobes due to the pressure from the peritoneal cavity. There were no secretions or plugs in the bronchi.

Discussion. Effect on Heart. Reid and Brace[9] have shown in a series of 35 patients that irritation of the respiratory tract by endotracheal intubation may be followed by a reflex effect upon the heart. While some of their electrocardiographic tracings are done on patients under cyclopropane anesthesia and may therefore be disregarded for our purpose, considerable changes in the electrocardiogram are found during intubation under nitrous oxide anesthesia, when the heart is not supposed to be more excitable than without anesthesia. Following normal sinus rhythm before insertion of the endotracheal tube, "regular auriculo-ventricular rhythm without P waves" appears after intubation. In another patient, the tracing of regular sinus rhythm is followed by marked bradycardia with blocked auricular extrasystoles. In a 3rd patient, regular sinus tachycardia is followed by many auricular extrasystoles and increased heart rate. The authors conclude that the respiratory passages seem to be potential foci for the origin of vago-vagal reflexes, which may be initiated by mechanical irritation, through catheters, Magill tubes, and the like. These reflexes may then produce either a narrowing of the coronaries with resulting decrease in myocardial blood flow, or induce profound alterations in the reaction of the specific tissues of the heart.

More recently, Burstein *et al.*[1] observed electrocardiographic disturbances in 73 out of 109 patients (68%) during endotracheal intubation. Control electrocardiograms were obtained in all patients prior to intubation. Only 6 of these patients were awake. In 3 of these 6 patients, electrocardiographic changes were noted. Two developed sinus tachycardia at a rate of 140 per minute with considerable depression of the RST segment. The 3rd patient developed paroxysmal tachycardia at a rate of 170 per minute and auricular fibrillation. Prolonged exploration and excessive instrumentation produced more severe changes. Patients with hypoxia before intubation and those with abnormal electrocardiograms before intubation developed more severe changes. All the cardiac changes in this series were transitory and of no grave importance, but the possibility of their occurance has to be kept in mind, and the patient has to be watched closely through the procedure.

Case 1 presents several interesting features. Despite the very poor condition of his coronary arteries, tracheobronchial aspiration was performed 11 times, with a very grave risk. But this risk had to be taken since the man "was drowning in his own fluids". Intubation through the nose was extremely easy and therefore, could be

repeated often. If it had been difficult, tracheotomy would probably have been indicated, to afford repeated suction. The question of leaving the Magill tube in place was considered, too, but the danger of causing laryngeal edema through the prolonged indwelling of the tube was considered too great. Foregger[4] reports a case in which a tube was left in place for several days (138 hours), but his patient had paralysis of the vocal cords, so no movement of the cords around the tube was present. Besides, the author's patient was very restless and excited and tried to remove the tube during the short period of aspiration.

Bronchoscopy was performed once in the beginning. It proved to be a very exhausting procedure to this patient, and since it was done soon after the first nasotracheal suction, it did not produce very satisfactory results. Therefore, repeated nasotracheal aspiration through the Magill tube was considered the method of choice.

Atelectasis. Spectacular results of tracheal aspiration are gained in cases of atelectasis developing after operations under general or spinal anesthesia.

Postoperative atelectasis can be largely avoided by adequately preparing the patient for operation, by careful premedication, by keeping the airway free during the operation, by encouraging the patient to move postoperatively (that is, to turn from side to side), by encouraging him to cough and take deep breaths or to cause forced deep breathing by CO_2 inhalation. Heavy sedation should be avoided.

The incidence of postoperative atelectasis is as high following spinal anesthesia as it is following general anesthesia. The type of operation seems more important than the type of anesthesia used. An added reason is probably that spinal anesthesia is frequently the method of choice in patients suffering from colds, asthma, and emphysema, conditions predisposing them to atelectasis (Cases 4 and 6).

Obstructive Dyspnea. Remarkable improvement has been observed following tracheobronchial aspiration in many cases of acute bronchiolitis, superimposed on chronic pulmonary disease. Obstructed, cyanotic patients, unconscious or semiconscious from want of oxygen, though lying in an oxygen tent, returned to consciousness and showed normal color and adequate respiratory exchange after just 1 tracheal aspiration.

Case 7 is interesting for several reasons: first, because of the seemingly remarkable recovery this man made with the combined treatment of tracheobronchial aspiration and helium–oxygen inhalation which seems especially indicated in these cases of obstructive dyspnea; and secondly, because it illustrates the sad fact that endotracheal aspiration is no cure-all. It relieves only cyanosis due to obstruction of the airway caused by secretions, inspissated material, or plugs of mucus. And these actually should be present and diagnosed before endotracheal suction is warranted in an extremely sick medical patient. This statement is made because, among a considerable series of cases of successful endotracheal suction in many kinds of other diseases such as unconsciousness due to accident, cerebral vascular accident, cerebral tumor, diabetic coma, there are only 2 cases which mar an otherwise excellent record (Cases 8 and 9). Neither of these 2 patients was dying from tracheobronchial obstruction. Nothing could have saved either one of these patients. But experiences like these emphasize the fact that endotracheal suction is not without danger and

should not be done without definite indication.

Pulmonary Edema. Acute pulmonary edema is not in itself an indication for endotracheal aspiration. In pulmonary edema, we are dealing with hindrance to the absorption of oxygen caused by the presence of fluid in the alveoli and by the edematous swelling of the alveolar walls. Positive pressure breathing, combined with the inhalation of oxygen-enriched atmospheres, tends to provide a positive pressure on the walls of the pulmonary capillaries and thereby opposes the tendency for serum to leak out. This is one of the recognized methods of treating pulmonary edema. It is conceivable that, by using endotracheal suction, the physical effect on the pulmonary capillaries might be in the opposite direction, so that the negative pressure on the walls of the pulmonary capillaries might be increased and more edema might be produced. Besides, in pulmonary edema caused by cardiac failure, the stress of the procedure and possible reflex reactions may strain the heart. This is particularly true in patients with recent myocardial infarction.

At the present time a study on the effect of ethyl alcohol inhalation in acute pulmonary edema is being conducted. As shown in animal experiments[7,8], ethyl alcohol vapor exerts a favorable action as an anti-foaming agent in acute pulmonary edema. Clinical tests demonstrated the applicability of this method to humans[10].

Analysis of State of Heart. Chronic coronary insufficiency is often combined with emphysema, bronchiolitis, and other chest conditions. In the event that retained secretions are diagnosed, a careful analysis of the state of the heart has to be made before instituting tracheobronchial aspiration, if the secretions are only a minor part of the general trouble. On the other hand, in the presence of atelectasis, tracheobronchial suction should be instituted immediately, and the same is true whenever retained secretions are endangering the patency of the airway, especially in an unconscious or paralyzed patient.

The anesthesiologist, when asked to perform endotracheal aspiration, should be regarded as a consultant, not as a technician called in for his skill to perform a certain procedure. He should be in a position to advise against the procedure, or at least to discuss it with the attending physician, and be informed or be given time to inform himself adequately about the condition of the patient.

The fact that a patient is cyanotic and his air passages obstructed is in itself not an indication for tracheal aspiration. Insertion of a simple pharyngeal airway may be all that is needed to relieve an obstruction caused by relaxed pharyngeal structures. Laryngeal edema may be the cause of obstruction, and if not diagnosed, may be made worse by attempts to pass a tube blindly into the trachea.

Summary and Conclusion. Endotracheal aspiration is often a life-saving procedure. It should be done with skill and care. It should not be made a routine procedure and left to the intern or the nurse. Definite diagnosis of chest disease should be made, namely, atelectasis, purulent bronchiolitis with inability to cough up secretions, or definite inability to cough and bring up secretions in a weakened or paralyzed patient, where tracheal râles, ronchi, wheezing, or otherwise unexplained cyanosis are present.

An effort should be made to decrease the possible vago-vagal effect on the heart by administering adequate doses of atropine beforehand, if not otherwise contraindicated, in patients with a structurally altered heart. Intravenous procaine or pronestyl by mouth

could be cautiously tried to decrease cardiac irritability before intubation in those patients who suffer from arrhythmias, auricular fibrillation, or heart block.

In unskilled hands, this procedure may be followed by several complications. Indwelling endotracheal tubes may be used in adults with due precautions for a limited time, if practically constant suction is necessary, but in infants and children tracheotomy is preferred, because of the ever-present danger of causing laryngeal edema and pressure necrosis by leaving the endotracheal tube in place.

Tracheobronchial aspiration through a wide-bore rubber tube can be performed effectively as a bedside procedure in the severely ill patient with retained tracheobronchial secretions.

Nine cases are presented and discussed.

Indications, precautions, and limitations are stressed.

REFERENCES

1. **Burstein, C. L., Lo Pinto, F. I.,** and **Newman, W.**: Anesthesiology, **11**, 224, 1950.
2. **Cardon, L.**: J. Am. Med. Assn., **142**, 1039, 1950.
3. **Foregger, R.**: Ibid., **133**, 1200, 1947.
4. Idem: Anesthesiology, **7**, 285, 1946.
5. **Haight, C.**: Ann. Surg., **107**, 218, 1938.
6. **Kuehn, F.**: Zntrlbl.f.Chirurgie, **39**, 73, 1912.
7. **Luisada, A. A.**: Proc. Soc. Exper. Biol. & Med., **74**, 215, 1950.
8. Idem: Circulation, **2**, 872, 1950.
9. **Reid, L. D.,** and **Brace, D. E.**: Surg., Gynec. & Obstet., **70**, 157, 1940.
10. **Weyl, R., Luisada, A. A.,** and **Goldmann, M.**: Am. Heart Assn. Meeting, 1951: In press.

A DEVICE FOR OBJECTIVE CLINICAL MEASUREMENT OF CUTANEOUS ELASTICITY: A "PINCHMETER"

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The usual clinical estimate of cutaneous elasticity is made by digital pinching. However informing this may be in such acute states as dehydration, such an estimate is of little value in conditions which persist and vary over long periods, or when the comparative estimates are made by different individuals. The purpose of this note is to describe an instrument which enables objective, quantitative evaluation of skin elasticity. Since the mechanism of this device simulates that of a digital pinch, it is called a pinchmeter.

Principles and Construction. The only other apparatus described for this purpose is that of Schade[3], which is an adaptation of the Schiotz impression tonometer. It has been modified by Kirk and Kvorning[2]. This apparatus is inconvenient in use. It measures the turgor of skin and subcutaneous tissue rather than the elasticity of the dermis as such.

The chief sensory impression in digital pinching is one of resistance to the attempt to draw together the areas of skin under examination. Both the force applied and the spatial effect of this force enter into the estimate of resistance. In the "pinchmeter" herein described the applied force and the skin area between the two test points are held constant. Cutaneous displacement is registered on a dial micrometer to 0.02 of the distance between the test points. The temporary attachment of the instrument to the skin is made by the minute atraumatic stainless steel teeth taken from the ½ inch constant traction bandage of Gardner[1]. The length of the skin "bite" is 1 inch, and the force applied by the spring which tends to return the instrument's pointer to zero position is 100 gm. The meter is adapted from a standard dial indicator pocket micrometer*. The construction† is shown in Fig. 1.

Clinical Use. The use of the apparatus is illustrated in Fig. 2. The traction teeth are moved to open position by sliding back lever A. Skin contact is made by resting the points lightly against the area to be tested. Lever A is then released so that a 100-gm. tensional force is applied to the skin. The instrument is held balanced lightly and slowly vibrated to insure that its own weight is not affecting the pointer position. The skin elasticity coefficient is then read from the dial. With a little practice, this process takes less than 5 seconds. The slow flow of skin under stress described by Kirk and Kvorning[2] does not interfere in this brief procedure.

Readings are compared with a table of normal values made for various sites and different age groups in normal subjects. Values differ for different sites. Thus, skin tension may vary fourfold or more as between breast and

*Starret #1010, 0 to 3/8 in.

† The pinchmeter may be obtained from Mr. Fred Hartnett, 12720 Lakeshore Blvd., Cleveland 8, Ohio.

shin. A thorough examination of the entire body surface includes about 70 measurements, but often these can be limited to selected areas, such as forearm, forehead, cheek, hands, ankles, and feet. Two determinations are made at each site, the second at right angles to the first. The results are averaged.

Skin elasticity is scored in multiples of normal values. The ratio rarely ex-

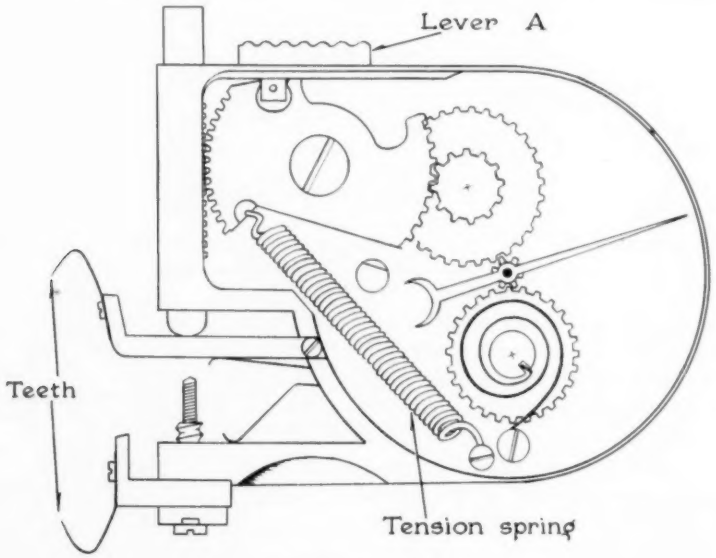

FIG. 1.—Mechanism of pinchmeter.

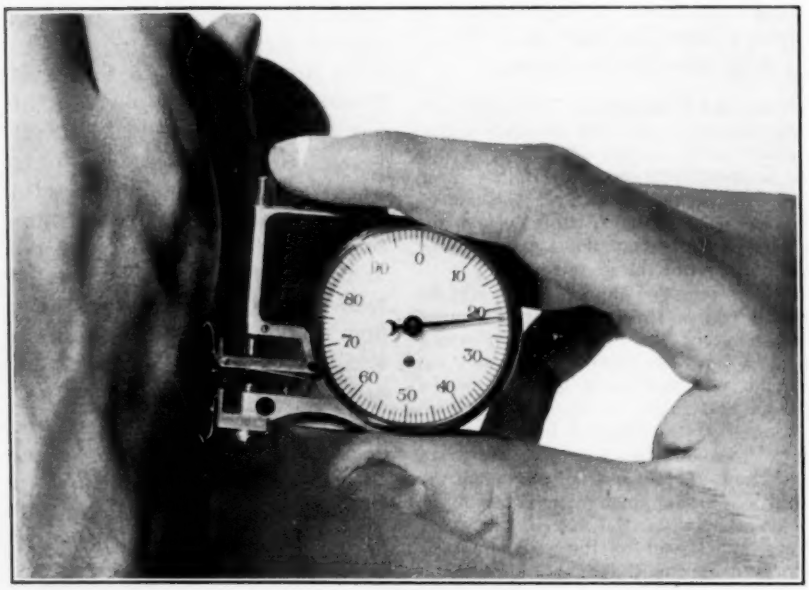

FIG. 2.—Application of pinchmeter.

ceeds 8. It can be measured to small fractions of a whole number, but such accuracy has not been found necessary in clinical studies.

Fig. 3 illustrates measurements made in a case of Buschke's scleredema at intervals of 1 year. This 17-year old girl was at first thought to suffer from scleroderma. A biopsy was inconclusive. The facts that elasticity measurements increased from the head downward and that there was spontaneous remission established the diagnosis as scleredema.

The instrument has been a means of predicting, within a few hours after starting treatment with cortisone or ACTH, the response to be expected in cases of scleroderma. It has also been used in a study of the effect of these agents on cutaneous elasticity in patients without dermatological disease.

The quantitative study of skin elasticity in conditions such as dehydration and edema, endocrine disease and ageing, are examples of the many possible applications of this instrument.

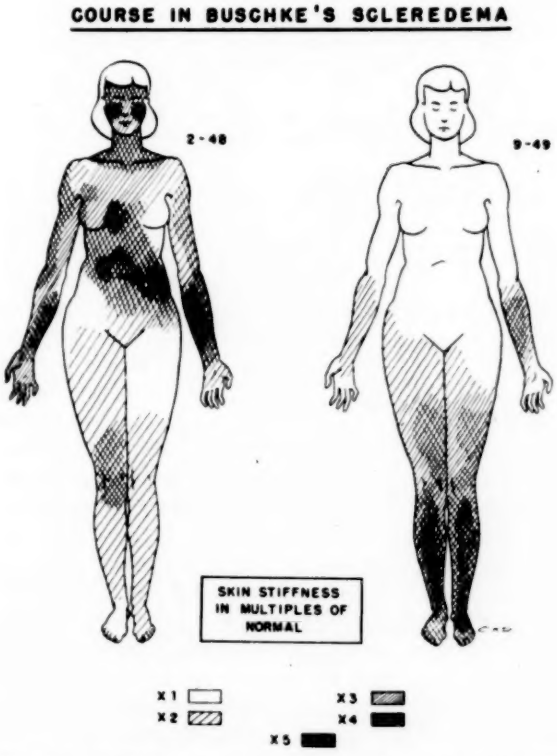

FIG. 3.—Relative elasticity measurements in scleredema over 19 months.

REFERENCES

1. **Gardner, W. J., and Seitz, V. B.:** Am. J. Surg., **70,** 232, 1945.
2. **Kirk, E., and Kvorning, S. A.:** J. Gerontol., **4,** 273, 1949.
3. **Schade, H.:** Ztschr.f.exper.Path.u.Therap., **11,** 369, 1912.

THE PREVENTION OF ACUTE ANOXIC ANOXIA BY MEANS OF DISPERSION OXYGENATION OF BLOOD

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In all conditions where the diffusion of oxygen through the alveolar membranes of the lungs is impeded, rapid deterioration of the central nervous functions results. Respiratory arrest is followed shortly by cardiovascular crises, ending in death.

In clinical conditions with reduced vital capacity and pulmonary minute-volume, such as pneumonia, pulmonary edema, massive atelectasis, and paralysis of the respiratory muscles or the respiratory center, the active or passive inhalation of gas mixtures with high oxygen tension is a life-saving procedure. If, however, pulmonary disease has progressed to the point where the diffusion of oxygen is limited to a small area of intact alveolar epithelium so as to make full oxygenation of pulmonary arterial blood impossible, then inhalation methods become ineffective and another means of blood oxygenation has to be sought.

In the present experimental investigations, extreme anoxic anoxia has been produced by eliminating oxygen exchange in the lungs by various procedures and by mechanically pumping and oxygenating the venous blood in an extracorporeal circuit.

The idea of oxygenating the circulating blood outside the body by artificial means is not new, and a great number of oxygenators have been devised during the past 80 years. Björk[2] has provided us with an excellent review of this subject.

In the early attempts to oxygenate blood, air or oxygen was bubbled through blood[17] or blood was exposed to oxygen by various procedures. The slowness of the oxygenation, however, as well as the development of foam made all these methods impractical for the continuous perfusion of large volumes of blood. During this century, various instruments have been constructed which spread thin films of blood over large stationary or moving surfaces and expose the blood in this way to oxygen[1-3,7-9,11-13,16,18]. These recent attempts more or less imitate the physiological mechanism of gas exchange in the lungs. The more nearly human proportions are approached, however, the more formidable becomes the task of pumping approximately 6 liters of blood per minute over large surfaces exposing it to oxygen, and returning the oxygenated blood to the body, without causing hemolysis. It would seem to be beset with technical difficulties of such magnitude that the application of these devices for human use would, as yet, be remote.

Method. The oxygenator used in the present study[5,6] is based on an old principle of

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oxygenating blood in the laboratory, namely, by bubbling the gas through it. Fig. 1 is a schematic drawing of the apparatus which has been described in previous publications. By forcing the oxygen under pressure through a porous membrane, such as a bacterial filter, a huge interface between the venous blood and the innumerable tiny gas bubbles is created. In this way very rapid and full oxygenation is insured. This dispersion of oxygen in blood is then resolved by making the "mist" of oxygen bubbles coalesce into large bubbles by means of a silicone antifoam compound coated on glass beads. The excess gas is then allowed to escape in a bubble trap and the oxygenated blood is pumped back to an external jugular vein.

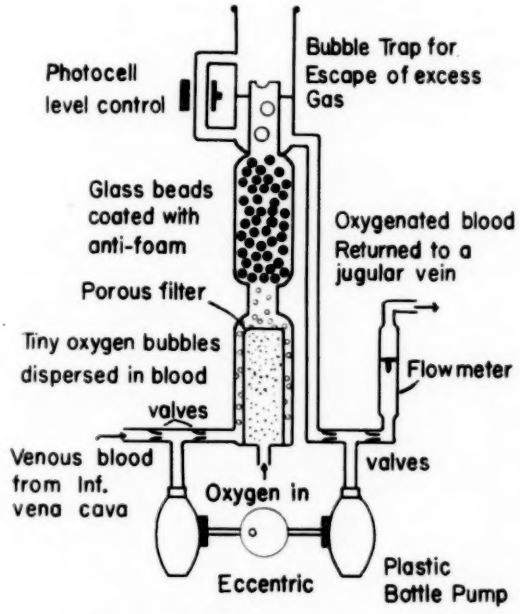

FIG. 1.—Diagram of the apparatus used for oxygenation and circulation of the blood.

In all experiments to be described, dogs were prepared with morphine–atropine and only local anesthesia was used for the introduction of a polyethylene catheter into the vena cava inferior, via a femoral vein, for the withdrawal of venous blood. A cannula in an external jugular vein was used for the return of the oxygenated blood. Paritol (30 mg./kg.) was used as an anticoagulant and protamin sulfate (2 mg./kg.) as an agent to neutralize the anticoagulant after the experiment. Arterial blood pressure was recorded from a carotid artery; respiratory movements, with a pneumograph; and blood flow through the apparatus, with a rotameter. No studies on possible chemical changes of the blood were made in the present investigations. Only the way in which acute anoxia was produced varied from one type of experiment to the other.

BILATERIAL PNEUMOTHORAX. A tightly fitting mask consisting of a plastic funnel and dental dam was put over the shaved head of the dog and connected with a spirometer to measure the respiratory volume before and during the experiment. After a satisfactory blood flow (a minimum of 40 cc./kg./min.) was obtained in the extracorporeal circuit and the blood appeared fully oxygenated, a 20-gauge needle was inserted into the pleural cavity. The needle was then connected with a rubber tube leading to a nitrogen tank and this gas was introduced into the pleural cavity under pressure. About 2 minutes were required to collapse each lung successively. The rubber tube was then clamped by a hemostat to avoid subcutaneous emphysema on withdrawal of the needle. In case the reading on the spirometer scale still indicated a small volume of pulmonary ventilation, more nitrogen was introduced into the pleural cavity in order to abolish any appreciable inflation of the lungs. This was accomplished in all

animals except in dogs labeled Nos. 110, 113, and 114, in which the minute-volume was reduced to 25, 16, and 8 cc./min., respectively. Since the weights of these animals were 13.6, 9.0, and 10.0 kg., these small minute-volumes could not have appreciably alleviated the severe acute anoxia. At the moment of complete collapse of both lungs the animals became restless, but as the blood flow was established they quieted down and remained still for the duration of the experiment. Table 1 shows the changes in respiratory rate, pulse rate, and blood pressure.

The 20-gauge needles were again inserted into the pleural cavity and the nitrogen was removed by suction. The needles were withdrawn when the respiratory minute-volume of the animals returned to its normal value.

TABLE 1.—BILATERAL PRESSURE PNEUMOTHORAX AND ARTIFICIAL OXYGENATION

Dog No.	Weight kg	Duration of pulm. collapse min.	Mean blood flow cc./kg./min.	Mean respiration r/min.		Mean pulse b/min.		Mean blood pressure mm.Hg	
				before	during	before	during	before	during
92	6.8	45	58	16	12	132	200	85	60
93	7.3	34	62	12	4	144	96	140	100
94	9.0	30	55	10	40	126	204	100	60
95	8.6	29	57	12	18	180	200	145	60
97	6.8	37	58	17	50	160	160	90	90
98	4.0	30	31	15	23	126	135	95	85
100	6.3	49	71	14	18	108	114	95	90
101	5.9	33	38	30	15	114	132	105	130
103	5.0	13	30	19	9	114	150	60	55
109	6.3	33	63	40	6	120	66	60	50
110	13.6	29	32	22	11	120	58	150	120
111	10.5	31	48	24	22	100	120	130	140
113	9.0	31	50	32	22	84	120	110	145
114	10.0	31	50	14	8	120	66	80	85
115	11.3	40	40	14	32	60	100	125	96

In most cases, the minute volume was increased for a short period due to temporary hyperventilation. After removal of the catheter from the inferior vena cava and of the cannula from the external jugular vein and carotid artery, the skin incisions were sutured. These animals, when lifted from the board and placed on the floor, stood up, walked, responded to call, and, except for the drowsiness due to morphine sedation, behaved in a normal way. Control animals treated in exactly the same way as outlined above except for the bubbling of oxygen through the extracorporeal circuit died in acute anoxia within 10 minutes.

Paralysis of Respiratory Muscles. The availability of highly purified curare-like compounds makes it possible to standardize acute anoxic anoxia due to paralysis of the respiratory muscles. Dihydro-beta-erythroidine (1.5 mg./kg.) and d-tubocurarine chloride (0.25 mg./kg.) were used successfully in the experiments to be described. By a single intravenous injection of these compounds, in the doses indicated, respiratory paralysis was achieved in about 30 seconds. If artificial oxygenation was started before the injection of the paralyzing agent, spontaneous recovery of the respiratory movements occurred in less than 5 minutes. In order to prolong the period of respiratory arrest and thus test the efficiency of the oxygenator, the initial dose of the curare-like compounds was injected repeatedly whenever abdominal respiration appeared to return. In this manner, it was possible to extend the period of complete respiratory arrest to more than one hour while the blood was being circulated and oxygenated outside the body. The information in Table 2 reveals that, following respiratory arrest, all signs of cardiovascular crises and vasomotor collapse could be prevented. In all cases the artificial oxygenation of blood was continued until respiration was judged to be normal.

Paralysis of Respiratory Center. It was of physiological and clinical interest to determine if acute anoxia due to another mechanism could also be overcome by artificial oxygenation of the blood. Paralyzing of the respiratory center was chosen as the experimental technique.

In morphinized dogs, relatively small doses of sodium pentothal produce medullary paralysis. The dogs in this series of experiments received 2 mg. of morphine per kg. subcutaneously and repeated doses of intrave-

nously administered sodium pentothal. Starting with 200 mg. of sodium pentothal as an initial dose, as little as 50 mg. after longer intervals was sufficient to prolong respiratory arrest in experiments which lasted as long as 38 minutes. After each injection, the arterial blood pressure dropped to extremely low values and stayed at these levels throughout the experimental period of medullary paralysis and artificial blood oxygenation. The blood pressure readings (Table 3) were taken from the continuous recordings just before the first voluntary respiratory movement. After respiration and blood pressure approached normal levels, the circulation of the oxygenated blood was stopped, the catheter and cannulas removed, the opened blood vessels ligated, and the skin incisions sutured. Due to the deep morphine sedation and the large doses of sodium pentothal, it took several hours before the animals recovered from the anesthesia.

In another series of experiments, respiratory arrest was induced by deep ether anesthesia. The morphinized animals were made to breathe a high concentration of ethyl ether through a tightly fitting mask. The respiratory rate slowed down somewhat, but respiratory arrest did not occur even when the inhaled gas was fully saturated with ether. The explanation for this failure to produce respiratory paralysis by inhalation of a high concentration of ether lies in the fact that volatile ether escaped from the blood in the bubble trap of the oxygenator at a very rapid rate and therefore the high ether blood levels necessary for respiratory paralysis could not be reached. For this reason 1 or 2 cc. of ether were slowly injected intravenously until respiratory arrest did occur. Under the conditions of these experiments the effect of this small amount of intravenous ether did not last longer than about 3 minutes. Therefore,

TABLE 2.—PARALYSIS OF THE RESPIRATORY MUSCLES AND ARTIFICIAL OXYGENATION

Dog No.	*Weight kg.*	*Duration of resp. arrest min.*	*Blood flow cc./kg./min.*	*Mean blood pressure mm.Hg*		*Mean pulse b/min.*	
				before	*during*	*before*	*during*
118	10.0	49	42	110	60	120	176
119	5.4	69	37	130	80	104	96
120	15.0	20	22	110	136	60	60
121	11.0	25	44	130	130	140	120
123	10.0	30	40	120	120	140	90
124	11.7	20	44	85	90	80	110
125	3.6	35	48	70	100	130	120
126	8.5	27	45	100	110	120	120
127	6.8	19	41	115	65	120	110

TABLE 3.—PARALYSIS OF THE RESPIRATORY CENTER BY ANESTHETICS AND ARTIFICIAL OXYGENATION

Dog No.	*Weight kg.*	*Duration of resp. arrest min.*	*Mean blood flow cc./kg./min.*	*Mean blood pressure mm.Hg*	
				before	*during*
Sodium Pentothal					
129	7.3	35	55	130	10
131	11.3	16	33	95	40
132	17.2	38	40	125	60
Ethyl Ether					
140	5.0	8	75	135	50
141	13.5	19	37	100	45
146	12.6	8	32	95	50

respiratory arrest was maintained by slow infusion of ether.

The blood pressure stayed at about 50 mm. of Hg throughout the experiments and did not drop to the low readings found immediately after the injection of sodium pentothal. After the last injection of ether, it took several minutes before respiratory movements recurred. Shortly afterwards, the eye reflexes could be elicited and after about 15 min. the animals regained full consciousness.

Discussion. The availability of an efficient oxygenator which can substitute for the function of the heart and the lungs presents the possibility of preventing or relieving the most severe degrees of anoxic or stagnant anoxia. Previous experiments with dogs inhaling pure nitrogen for prolonged periods of time while their blood was pumped and oxygenated outside the body[5,6] have shown that a complete deprivation of oxygen from the inspired air can be overcome and survived without any remaining signs of cerebral damage. This experience encouraged the present investigations in which various acute anoxic conditions were tested as model experiments for situations encountered in clinical medicine. It should be emphasized, however, that at present this discussion must be considered of a more speculative nature and that only the eventual application of the described oxygenator in clinical conditions of anoxic and stagnant anoxia will determine its value.

The abolition of pulmonary ventilation by bilaterial pressure pneumothorax constitutes such a severe degree of acute anoxia that its counterpart in medical practice may be found only in accidents with acute obstruction of the airways or pulmonary embolism. Longer lasting and less pronounced degrees of anoxic anoxia constitute a large variety of pulmonary pathology such as pneumonia, edema, emphysema, asthma, and partial obstruction of the air passages.

The experimental procedure of paralyzing the respiratory muscles with curare-like compounds was chosen rather for the purpose of testing the efficiency of the described oxygenation method than for its clinical applicability. It is not suggested that oxygenators take the place of respirators in acute poliomyelitis.

It is not difficult, however, to envisage a clinical application of artificial oxygenation in conditions of medullary paralysis. This seems to be particularly desirable in bulbar poliomyelitis. Recent investigations have shown that anoxia plays a much more important role in the symptomatology and the progressive destruction of medullary centers than had been previously assumed[1,10,14]. In fact, some symptoms of bulbar poliomyelitis, such as hyperexcitability, muscular tremors, confusion, irritability, somnolence, coma, and convulsions in children, can usually be overcome by early and adequate oxygen therapy by means of tracheotomy[15]. The mortality (83%) in the group of patients with involvement of the circulatory center is higher than in the group with impaired respiratory center. Since the impression was gained that the circulatory disturbances resulting from medullary paralysis were contributing factors in the production of the hemorrhagic pulmonary edema, making further inhalation of oxygen impossible[4], the thought of artificial oxygenation of the cerebral or the systemic circulation in these desperate cases is very attractive.

The chances for resuscitation and survival seem even better in conditions of acute medullary paralysis where the neurons have not been damaged previously by anoxic episodes or inflammatory or edematous changes. Respiratory arrest and vasomotor collapse due to accidents in deep surgical anesthesia or in too high spinal anesthesia may lend themselves to success-

ful treatment, by pumping oxygenated blood into the arterial tree. The same reasoning may hold true for the most severe conditions of asphyxia of the newborn, where perfusion with oxygenated blood may even be possible through the umbilical cord.

Summary. Possible applications of a newly devised instrument for the oxygenation and circulation of blood outside the body have been explored in dogs under various experimental conditions:

1. In 15 animals, acute anoxic anoxia produced by bilateral pressure pneumothorax could be prevented by means of the oxygenator.

2. Complete paralysis of the respiratory muscles produced in 9 dogs by curare-like compounds did not result in acute anoxia as long as their blood was being oxygenated artificially.

3. By means of repeated injections of sodium pentothal or ethyl ether, respiratory and vasomotor paralysis produced in 6 dogs was overcome by artificial oxygenation of their blood.

4. Some of the clinical implications of these experiments are discussed.

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REFERENCES

1. **Bayliss, L. E., Fee, A. R.,** and **Ogden, E.**: J. Physiol., **66,** 443, 1928.
2. **Björk, V. O.**: Acta Chir. Scand., **96,** Suppl. 137, 1948.
3. **Bornstein, A.**: Arch. Exp. Path. Pharm., **115,** 367, 1926.
4. **Brown, J. R.,** and **Baker, A. B.**: J. Nerv. Ment. Dis., **109,** 54, 1949.
5. **Clark, L. C., Gollan, F.,** and **Gupta, V. B.**: Science, **111,** 85, 1950.
6. **Clark, L. C., Gupta, V. B.,** and **Gollan, F.**: Proc. Soc. Exp. Biol. and Med., **74,** 268, 1950.
7. **Cruikshank, E. W. H.**: J. Physiol., **82,** 26, 1934.
8. **Daly, I. de B.,** and **Thorpe, W. V.**: J. Physiol., **79,** 199, 1933.
9. **Euler, U. S. von,** and **Heymans, C.**: J. Physiol., **74,** 2, 1932.
10. **Galloway, T. C.**: J. Am. Med. Assn., **123,** 1096, 1943.
11. **Gibbon, J. H., Jr.**: Arch. Surg., **34,** 1105, 1937.
12. **Jongbloed, J.**: Ned. Tijdschr. Geneesk., **92,** 1065, 1948.
13. **Karlson, K. E., Dennis, C.,** and **Westover, D. E.**: Proc. Soc. Exp. Biol. and Med., **70,** 223, 1949.
14. **Kubicek, W. G., Holt, G. W.,** and **Kottke, F. J.**: Arch. Physical Med., **29,** 84, 1948.
15. **Minnesota Poliomyelitis Res. Comm.**: J. Am. Med. Assn., **135,** 425, 1947.
16. **Richards, A. N.,** and **Drinker, C. K.**: J. Pharm. Exp. Ther., **7,** 467, 1915.
17. **Schröder, W.**: Arch. Exp. Path. Pharm., **15,** 364, 1882.
18. **Thomas, J. A.**: J. de Phys., **40,** 123, 1948.

THE EFFECT OF DIBULINE ON NOCTURNAL GASTRIC SECRETION OF ULCER PATIENTS

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It was shown previously[6] that the subcutaneous administration of dibuline* in doses of 20 to 60 mg. to peptic ulcer patients produced approximately a 75% decrease in the volume of interdigestive gastric secretion for an average of 96 minutes. We concluded that the relative brevity of its depressant action detracts from its value as an ideal acid inhibitor. However, because of its effectiveness and lack of toxicity, it was decided to test the action of dibuline as an inhibitor of nocturnal gastric secretion, since this portion of the gastric secretory activity is often difficult to control. A preliminary investigation had indicated that the drug has a potent inhibitory action on night secretion in peptic ulcer patients[5]. In these studies its effectiveness was compared with that of atropine.

Material and Method. Twelve men with proved active duodenal ulcers were selected from the gastrointestinal clinic and from the medical wards of this hospital (Table 1). Nine had had a complication of the disease. Their average age was 40, average duration of symptoms was 8½ years, and they were equally divided between the white and Negro races. Each was admitted for a period of at least 6 days and all were fed a bland, low residue diet every 2 hours between 7 a. m. and 4 p. m. daily. At 6:45 p. m., a No. 16-French Levin tube was introduced into the gastric antrum with fluoroscopic observation and the gastric residuum was evacuated. Continuous aspiration was maintained from 7 p. m. to 7 a. m., the collection bottles being changed at hourly intervals. On successive nights, subjects received subcutaneous injections at 3-hour intervals of: (Night 1) 3 cc. of saline solution†; (Night 2) 40 mg. of dibuline[a]‡; (Night 3) 1 mg. of atropine sulfate[b]‡; (Night 4) 3 cc. of saline solution. On the 5th night, 40 mg. of dibuline[c]‡ were administered every 4 hours. No other medication was allowed during the test period of hospitalization. Analysis of specimens included determinations of free and total acidity (titration with 0.05-N. sodium hydroxide using Topfer's reagent and phenolphthalein as indicators), pH (Beckman pH meter), chlorides (Wilson and Ball)[10], and pepsin (Nirenstein and Schiff's modification of Mett method)[8].

Drug effects were compared with the averages of the 2 control nights, except in 3 instances where only 1 night served as a control.

Results. 1. Volume. Administration of both dibuline and atropine resulted in a striking reduction in volume of

* Dibuline was formerly called dibutoline. We are indebted to Merck and Co., Inc., Rahway, N. J., for generous supplies of the drug.

† Dibuline preservative solution containing no dibuline was substituted for saline solution on some control nights.

‡ To be subsequently referred to as: a = dibuline-3 or D-3; b = atropine-3 or A-3; c = dibuline-4 or D-4.

gastric contents obtained during the 12-hour test period (Table 2). Average decreases in gastric secretion were 75% (range 65 to 92%), 72% (range 49 to 82%), and 61% (range 44 to 71%), respectively, for dibuline-3, atropine-3, and dibuline-4. An average volume of secretion of 1068 cc. (range 795 to 1747) obtained on control nights was reduced to 270 cc. (range 61 to 479), 293 cc. (range 146 to 532), and 405 cc. (range 209 to 586) by the administration of dibuline-3, atropine-3, and dibuline-4, respectively (Table 3). No

TABLE 1.—SUMMARY OF CLINICAL DATA IN 12 ULCER PATIENTS GIVEN DIBULINE TO CONTROL NOCTURNAL GASTRIC SECRETION

Case	*Age*	*Color*	*Duration of ulcer in years*	*Complication of ulcer*
1	41	W	7	perforation
2	33	W	15	hemorrhage
3	44	C	4	chronic perforation
4	34	C	4	hemorrhage
5	34	W	8	intractable
6	26	C	10	partial obstruction
7	61	W	15	—
8	44	C	14	—
9	28	W	13	perforation
10	39	C	8	—
11	42	W	2	perforation
12	54	C	2	partial obstruction hemorrhage

TABLE 2.—EFFECT OF SUBCUTANEOUS ADMINISTRATION OF DIBULINE AND ATROPINE ON 12-HOUR NOCTURNAL GASTRIC SECRETION. PERCENTAGE DECREASE IN VOLUME, FREE ACIDITY, CHLORIDE, AND PEPSIN OF CONTROL NIGHTS

(See text and footnote, page 82, for definition of D-3, A-3, and D-4)

	Volume (cc.)			*Free Acid (mg.)*			*Chloride (mg.)*			*Pepsin × 10²*		
Case	*D-3*	*A-3*	*D-4*	*D-3*	*A-3*	*D-4*	*D-3*	*A-3*	*D-4*	*D-3*	*A-3*	*D-4*
1	74	78	71	86	91	84	74	78	70	76	82	70
2	69	82	59	73	96	73	70	81	58	57	87	54
3	76	80	63	81	97	92	74	82	76	78	87	86
4	68	66	59	80	77	41	63	63	54	80	78	65
5	70	77	59	80	85	68	71	80	59	65	72	52
6	84	77	57	97	97	76	88	90	59	85	95	76
7	92	81	63	82	79	93	93	84	65	88	83	80
8	87	49	44	93	69	43	88	51	43	93	71	55
9	73	81	71	79	86	73	74	81	68	69	71	72
10	65	64	57	73	99	52	64	67	53	76	91	61
11	78	68	73	96	90	66	77	58	70	92	88	90
12	68	62	67	78	75	72	64	59	66	72	67	71
					STATISTICAL ANALYSIS							
Mean	75	72	61	83	87	69	75	73	62	78	81	69
Standard Deviation	8.4	10.2	8.0	8.2	9.9	17	9.6	12.6	9.2	10.9	9.2	11.7
Probability* D-3 *vs.* A-3	>0.4	<0.5		>0.2	<0.3		>0.6	<0.7		>0.4	<0.5	
A-3 *vs.* D-4	>0.001	<.01		>0.001	<0.01		>0.02	<0.05		>0.02	<0.01	
D-3 *vs.* D-4	<0.001			>0.02	<0.05		>0.001	<0.01		<0.05		

* Probability that the difference of the means between the two groups is not due to chance. A value of less than 5% (0.05) in this report is considered to be statistically significant.

statistical difference in reduction of total output was noted between dibuline[-3] and atropine[-3], but both produced decreases in volume significantly greater than with dibuline[-4].

In order to ascertain if there was any difference in effect between the whole 12-hour test period and the last 9 hours, the latter allowing for completion of the gastric phase of secretion, volume output was calculated for the last 9 hours (Table 4). Reductions in volume output for the 12 and 9-hour periods were practically identical.

Differences in the volumes obtained on control nights (first and fourth) in 9 of the 12 subjects varied from 3 to 28% and averaged 14%. A comparison of volumes obtained on these 2 nights shows no difference of statistical significance (Table 5). This indicates reliable repeatability of the tests and no carry

TABLE 3.—TOTAL 12-HOUR NOCTURNAL GASTRIC OUTPUT, RESPONSE OF VOLUME, FREE ACIDITY, CHLORIDE, AND PEPSIN TO THE SUBCUTANEOUS ADMINISTRATION OF SALINE SOLUTION, DIBULINE, AND ATROPINE

Case	Saline Solution				Dibuline 40 mg. 3rd hr.				Atropine Sulfate 1 mg. 3rd hr.				Dibuline 40 mg. 4th hr.			
	Volume (cc.)	Free Acid (mg.)	Chloride (mg.)	Pepsin × 10	Volume (cc.)	Free Acid (mg.)	Chloride (mg.)	Pepsin × 10	Volume (cc.)	Free Acid (mg.)	Chloride (mg.)	Pepsin × 10	Volume (cc.)	Free Acid (mg.)	Chloride (mg.)	Pepsin × 10
1	1067	2259	5002	5950	278	309	1280	1416	232	219	1088	1088	313	378	1496	1780
2	965	2038	4861	2405	302	551	1480	1039	178	128	912	311	399	469	2039	1100
3	1010	1791	4304	1992	244	346	1118	441	199	64	767	261	378	141	1049	271
4	975	347	3718	4935	312	71	1355	1012	331	80	1383	1068	399	204	1648	1706
5	1347	3670	7152	7170	400	735	2079	2524	305	533	1455	2002	553	1162	2938	3441
6	1048	1800	4966	6362	172	58	601	942	239	53	515	294	452	429	2033	1525
7	795	503	3522	2422	61	90	258	294	146	106	557	405	290	36	1266	486
8	1039	1221	5139	6010	141	87	580	439	532	385	2510	1778	586	698	2957	2736
9	1742	4511	7776	6367	479	967	2052	1998	338	627	1489	1824	504	1238	2521	1792
10	930	478	3923	3961	325	129	1425	970	332	6	1287	371	396	232	1835	1554
11	785	745	3016	2880	169	30	705	232	251	71	1273	349	209	251	911	288
12	1134	1760	4956	6032	363	384	1805	1687	435	447	2031	1961	378	664	1683	1733
AVERAGE	1008	1760	4861	4540	270	314	1061	1083	293	227	1273	972	405	492	1864	1534

TABLE 4.—PERCENTAGE DECREASE IN GASTRIC OUTPUT DURING THE LAST 9 HOURS OF NOCTURNAL SECRETION PRODUCED BY THE SUBCUTANEOUS ADMINISTRATION OF DIBULINE AND ATROPINE

Case	Dibuline 40 mg. 3rd hr.	Atropine Sulfate 1 mg. 3rd hr.	Dibuline 40 mg. 4th hr.
1	75	84	68
2	72	87	61
3	75	76	54
4	69	69	70
5	68	77	56
6	84	70	58
7	96	83	54
8	89	50	37
9	72	74	63
10	66	67	49
11	80	75	82
12	71	55	73
AVERAGE	76	72	60

over of the drug action from the 3rd to the 4th night.

2. Acidity. Reductions in acid output were slightly but not significantly greater than those for volume (Tables 2, 3). The average percentage decreases obtained after the subcutaneous administration of dibuline^{-3}, atropine^{-3}, and dibuline^{-4}, were 5[illegible] 87, and 69% respectively. Again the decreases produced by dibuline^{-3} and atropine^{-3} were statistically greater than those observed after administration of dibuline^{-4}. Although it was observed that these drugs may decrease the pH, in most instances they increased it.

3. Pepsin and Chloride. As was observed with acidity, decreases in total output of pepsin and chloride closely paralleled the reductions in volume (Tables 2 and 3). The average decreases over the controls were all statistically significant but no difference between the effect of dibuline^{-3} and that of atropine^{-3} was noted. Decreases in pepsin and chloride after

TABLE 5.—TOTAL VOLUME OUTPUT CONTROL NIGHTS IN RESPONSE TO THE SUBCUTANEOUS ADMINISTRATION OF SALINE

	Volume Output in cc.		*Percentage Difference*
Case	*Night 1*	*Night 4*	
1	1109	1025	−8
2	699	1088	+19
3	1010	Not done	—
4	988	961	−3
5	1347	Not done	—
6	1006	1089	+8
7	779	810	+4
8	1211	866	−28
9	1678	1806	+8
10	828	1032	+25
11	785	Not done	—
12	1025	1243	+21
Mean	1035	1102	
Standard Deviation	±291	±293	
P*	>0.6	<0.7	

*P—Probability. No statistical difference.

TABLE 6.—SIDE-EFFECTS FOLLOWING SUBCUTANEOUS ADMINISTRATION OF DIBULINE AND ATROPINE

	D^{-3}			*A*$^{-3}$			*D*$^{-4}$		
Case	*Xerostomia*	*Flush*	*Nervous Symptoms*	*Xerostomia*	*Flush*	*Nervous Symptoms*	*Xerostomia*	*Flush*	*Nervous Symptoms*
1	+			+++	++	++	+		
2	++			+++	++	++	+		
3	+			++		+	+		
4	+			++			+		
5	++			+++	+++	+++	+		
6	+			+++			+		
7	++			+++	++	+++	+		
8	++			+++		++	+		
9	+			++		+	+		
10	+			++		+	+		
11	+			++	++	++	+		
12	++			+++	++	++	+		

+ = mild
++ = moderate
+++ = severe

dibuline-3 and atropine-3 were statistically greater than after dibuline4.

4. Toxicity. Although the reductions in volume and constituents of the gastric juice were almost the same for dibuline-3 and atropine-3, the differences in toxicity between the two drugs were striking (Table 6). Xerostomia was the only complaint offered when dibuline was administered at 3-hour intervals and then it was only moderately troublesome to 2 subjects. When given at 4-hour intervals, dibuline did not produce any bothersome symptoms. Six subjects (50%) considered the xerostomia produced by atropine so annoying that they "wanted the treatments stopped." In all instances atropine-3 caused unpleasant oral symptoms ("thick tongue", "parched throat"). Six subjects complained of the facial flush produced by atropine, and in 9, some form of central nervous stimulation was experienced. The usual complaints were restlessness, anxiety, and dizziness. Two of the 9 became irrational for short periods of time. No after-effects were complained of when dibuline was employed, but 6 subjects had symptoms on arising after receiving atropine. Weakness, unsteadiness, "like being drunk" were the most frequent complaints. It should be noted that mydriasis and cycloplegia, if present, were not troublesome since the tests were run at night.

Discussion. The desirability of inhibiting or neutralizing nocturnal gastric secretion in ulcer patients is generally recognized. It has been shown that free acidity may be higher during sleep[2], and most investigators have demonstrated that nocturnal gastric secretion of ulcer patients is higher than in the normal. Though a pharmacological approach to the control of night secretion in ulcer patients has been sought, most investigators who have employed acid inhibitors have reported disappointing results.

Winkelstein[11] administered atropine (0.87 mg.) subcutaneously to 2 patients without beneficial results. The low dosage employed and the failure to re-administer the drug at suitable time intervals accounts for the poor results. The same may be said for the results of Voegtlin[9], who administered one dose of atropine (0.65 mg.) at 9 p.m. He reported some depression of acidity in 3 of 5 subjects. Mears[7] gave atropine (0.87 mg.) by proctoclysis at 3-hour intervals and obtained a reduction in volume output of more than 20% in 25 of 50 normals and in 12 of 15 patients with duodenal ulcer. He also noted decreases in free and total acidity. These mildly effective results are in keeping with the small dosage. The practicality of this route of administration is open to question.

Levin *et al.*[4] administered dibuline intramuscularly in doses of 10 mg. at 4-hour intervals during the night and obtained variable and transitory effects. Again, inadequate dosage undoubtedly resulted in drug failure. Kirsner and his co-workers[3] reported that atropine was not effective in influencing the nocturnal secretion in 4 subjects with intractable ulcer when employed in total dosage of 1 to 6 mg. during any one night. These investigators do not indicate the frequency or route of drug administration in all instances. The authors are unable to explain the lack of effectiveness of atropine in these patients when higher doses were used, especially since Avey and co-workers[1] have demonstrated that the subcutaneous administration of 1.2 mg. of atropine to ulcer patients will reduce interdigestive gastric secretion by 72% for 2 hours. The latter results are also in accord with random observations of the writers[5,6]. It is felt that the striking reductions in nocturnal gastric secretion produced by

dibuline and atropine in this study as contrasted with those just discussed may be attributed to the differences in dosage employed and frequency of drug administration.

The daytime frequent-feeding program and the nocturnal aspiration of gastric contents resulted in rapid relief of ulcer symptoms in the entire group. Three patients in this study who were considered to have "intractable" ulcer symptoms at the time of hospital admission obtained complete relief within 24 to 48 hours. These results lend support to the importance of combating night secretion in ulcer.

The statistically significant greater reduction in volume of secretion produced by dibuline-3 as contrasted with dibuline-4 suggests that the drug should be given at least at 3-hour intervals to obtain optimum effectiveness. Six patients with "intractable" symptoms due to duodenal ulcer subsequently treated with a daytime frequent-feeding program and given dibuline at 3-hour intervals during the night without intubation obtained complete relief of symptoms within 2 to 4 days. Although the necessity for frequent administration of the drug detracts from its value, those who have been benefited do not object to this feature. The ability of atropine similarly to affect night secretion is considered to be only of pharmacological interest, since its extreme toxicity in comparably effective dosage precludes its use.

Summary. 1. The intermittent subcutaneous administration of either dibuline or atropine to 12 patients with duodenal ulcer resulted in a striking reduction in volume of nocturnal gastric secretion in all instances.

2. Although reductions of volume output resulting from the administration of 40 mg. of dibuline and 1 mg. of atropine every 3 hours were similar, both were statistically more effective than 40 mg. of dibuline administered every 4 hours.

3. Reductions in gastric output of acid, chloride, and pepsin produced by the drugs closely paralleled the decreases in volume.

4. In the dosage range employed, atropine administration produced exceedingly troublesome side effects, whereas dibuline was well tolerated.

5. The relative lack of toxicity of dibuline plus its effectiveness, which is almost identical with that of atropine, recommends it as a suitable pharmacological tool for future comparison of gastric secretory inhibitors.

6. The beneficial effect produced upon the clinical course of these patients by nocturnal aspiration of their gastric contents lends further support to the importance of combating nocturnal gastric secretion in ulcer patients.

REFERENCES

1. **Avey, H. T., Musick, V. H., Hopps, H. C.,** and **Hellbaum, A. A.:** Gastroenterology, **14,** 386, 1950.
2. **Hillenbrandt, F. A., Tepper, R. H., Grant, H.,** and **Catherwood, R.:** Am. J. Dig. Dis., **3,** 477, 1936.
3. **Kirsner, J. B., Levin, E.,** and **Palmer, W. L.:** Gastroenterology, **11,** 598, 1948.
4. **Levin, E., Kirsner, J. B.,** and **Palmer, W. L.:** Proc. Soc. Exp. Biol. & Med., **72,** 213, 1949.
5. **Lorber, S. H.,** Post Graduate Gastroenterology, edited by **Bockus, H. L.:** Philadelphia, W. B. Saunders Co., 1950.
6. **Lorber, S. H.,** and **Machella, T. E.:** Am. J. Med. Sci., **219,** 133, 1950.
7. **Mears, F. B.:** Surgery, **13,** 214, 1943.
8. **Nirenstein, E.,** and **Schiff, A.:** Arch. Verdauuengskrank, **8,** 559, 1902.
9. **Voegtlin, W. L.:** Gastroenterology, **9,** 125, 1947.
10. **Wilson, D. V.,** and **Ball, E. G.:** J. Biol. Chem., **79,** 221, 1928.
11. **Winkelstein, A.:** Am. J. Dig. Dis., **1,** 778, 1935.

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COMPLICATIONS OF BRONCHIAL ASTHMA

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CHRONICITY in asthma, as in all diseases, favors the development of complications, whether these be coincidental or caused by the disease. A search of the medical literature failed to yield any review articles on the complications of asthma. For this reason it seems desirable to refer to certain aspects of this problem which may be of concern to physicians.

THORACIC DEFORMITY. The type of thoracic deformity produced by uncontrolled asthma is conditioned by the patient's age. In the child, where the cartilages are soft and there is minimal ossification of the ribs, the sternum may be drawn inward, resulting in production of a concavity which may persist (*trichterbrust*). Later in childhood after the cartilage and bone have hardened to some extent, a pigeon breast may result. In forced inspiration a series of changes occurs. First, the upper ribs and manubrium are lifted upward and forward; next, the upper costal series becomes more nearly horizontal; most important of all is the diaphragm, which is contracting simultaneously. These factors lead in time toward a thoracic deformity characterized by a lateral "pulling in" of the ribs and protrusion of the sternum. The xiphoid process may form an acute angle with the body of the sternum. The anteroposterior diameter of the chest becomes greater than the side-to-side diameter. The clavicles often adapt themselves to the thoracic deformity and assume a horizontal position. A considerable amount of kyphosis may result. At times the scapula may be winged, though certain observers believe that the stooped posture of these children results in lateral displacement and upward and outer rotation of the scapulas with resultant increased prominence.

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In adults, the effect of long-standing asthma is production of the barrel-shaped chest, which is the result of severe emphysema, an inevitable accompaniment of protracted asthma. At first this bony deformity is transient, and at the end of the attack the lung empties itself and the chest resumes its normal contour. Later, the deformity becomes so pronounced as to be readily recognized even when the patient is fully clothed. According to Moll[87], as the lungs become overdistended, ribs do not show an overlapping as is normally seen in the anteroposterior roentgenogram, but they are raised and approach the horizontal position. This "ladder" effect is seen in children and in adults who have had asthma only a short time. In instances of prolonged asthma, a rounding of the chest involving mainly the 6 upper ribs is described. At the level of the diaphragm the chest is drawn in and the deep lateral sulcus is formed[87]. The extent of thoracic deformities produced is proportional to the duration of the disease and the intensity and frequency of attacks.

Rib Fractures. Most physicians who have seen a reasonable number of cases of bronchial asthma have seen instances of rib fracture following coughing in asthma. As Oechsli[90] pointed out, these fractures always occur in a diagonal line corresponding to the interdigitations of the serratus anterior and the external abdominal oblique muscles. Fractures occur in this region because of the opposed action of these muscles. They are often diagnosed first by roentgenography, although the pain produced should make one suspect their presence. A patient of Ginsburg's[41] had unexplained pain on the side of the chest opposite the site of fracture.

Bronchostenosis. Prickman and Moersch[97] directed attention to bronchostenosis as a complication of bronchial asthma. Stenosis of one or more bronchi was noted in 60 of 140 of their patients in whom bronchoscopy was done. In their cases the clinical picture was fairly typical. Cough is persistent and frequently paroxysmal, asthmatoid, and wheezing in character. Sputum may be profuse and may contain blood. Of greatest diagnostic significance is the development of fever and chills, more often fever alone, which is usually accompanied by definite leukocytosis. The physical signs are primarily those of unilateral atelectasis together with typical evidence of bronchial asthma or bronchitis. The roentgenographic observations are characteristic of atelectasis. Treatment consists of bronchoscopy with drainage. Dilation of the stenotic area is essential for adequate drainage.

Bronchiectasis. Whether or not the incidence of bronchiectasis is significantly increased in bronchial asthma is debatable. Watson and Kibler[131], for example, found bronchiectasis in 32% of their asthmatic patients, whereas Diamond and van Loon[24] found only 3 cases of asthma among 75 patients with bronchiectasis. An excellent discussion of the pathogenesis of bronchiectasis by Mallory[80] may cast some light on this question. He discussed 5 factors in relation to the pathogenesis of bronchiectasis: direct bronchial infection, congenital malformation of the bronchial tree, bronchial stenosis, pulmonary atelectasis, and pneumonitis, with its sequel, pulmonary fibrosis. He presented positive evidence that there is a causal relation in certain cases for each of these factors but no one of them is constant or can explain all cases. He concluded that acquired bronchiectasis is generally a disease of the pulmonary parenchyma as well as of the bronchial tree itself. Atelectasis may follow bronchial infection as a re-

sult of obstruction by mucopurulent secretions, a condition which Mallory[80] observed to be particularly prone to occur in infants and children because the collateral air circulation through the pulmonic alveolar vents (pores of Kohn) does not develop until adult life. In a group of 60 chronic asthmatic patients studied by Mallory[80], bronchiectasis was so exceptional that it appeared to be coincidental, although emphysema and cor pulmonale were common. Whereas patchy atelectasis is not unusual in bronchial asthma, it is generally of a reversible type, and this is the likely explanation of Mallory's observations. Some explanation other than the asthma itself is required for the incidence of bronchiectasis in the cases reported by Watson and Kibler[131].

A recent article by Waldbott and associates[130] suggested that the term "pseudobronchiectasis" be employed to designate a certain group of benign reversible processes for which surgical treatment is not indicated. As adequate follow-up bronchograms of the one patient presented in detail were not made and as there appears to be an insufficient number of patients improved roentgenologically, the authors hesitate to accept this term until further evidence is presented to justify its use.

Pulmonary Consolidation. There is a regrettable tendency to minimize the use of roentgenograms of the chest in the management of patients with bronchial asthma. Not only should a roentgenogram of the chest be made at the time of the initial study of the patient, but subsequent roentgenograms should also be made. This will aid in excluding conditions simulating asthma and on occasion will bring to light intrathoracic complications. Studies have shown that there is no significant difference in the incidence of acute infectious diseases in allergic and nonallergic persons. This applies to the acute pneumonitides in general. Certain types of pneumonopathies, however, are commoner in asthmatic persons than in the general populace. Thus, the bronchial obstruction of asthma is known to produce areas of atelectasis or even massive collapse. In a study of patients with bronchial asthma in whom pulmonary atelectasis developed, Cole and coworkers[19] pointed out that the diagnosis can be made with comparative ease if atelectasis is considered. They advocated roentgenography of the chest in the presence of sudden onset of thoracic pain with dyspnea and cough, and a pulse rate out of proportion to the temperature. Parenthetically, it may be said that thoracic pain, particularly localized, is not a manifestation but rather a complication of bronchial asthma. The interalveolar pores of Kohn which allow some passage of air may reduce the amount of atelectasis which would otherwise be present during the asthmatic attack. Miller and associates[85] believed that true allergic bronchopneumonia may occur and described 11 cases in children characterized by fever and frequently changing physical and roentgenographic signs.

Loeffler's[70] name is now attached to an often comparatively asymptomatic syndrome consisting of transient pulmonary consolidations, associated with leukocytosis and eosinophilia (as high as 60%). In the words of Apley and Grant[3], Loeffler's description of the radiologic observations is "embarrassingly comprehensive". He described shadows "in any position and in any size, of variable structure, homogeneous or more frequently patchy or cloudy, more or less sharply circumscribed, single or multiple, unilateral or bilateral". The consolidations usually last for only a few hours or at most for

several days and may be followed by involvement of other parts of the lungs. Most authors agree that Loeffler's syndrome is more likely to appear in allergic persons. This is not to say that asthmatic symptoms are an invariable part of the syndrome, for though all patients of Hansen-Pruss and Goodman[47] had severe intractable asthma, the summary by Wise[139] showed that only 5 to 8% of cases recorded in the literature had concomitant asthma. It is not clear whether Miller and associates'[85] "allergic bronchopneumonia" represents Loeffler's syndrome but it is the authors' belief that it does.

Tropical eosinophilia described by Weingarten[132] is characterized by infiltration of the lung, associated with paroxysmal cough, episodes of asthmatic breathing, anorexia, severe leukocytosis, and eosinophilia, which may be intense (reaching 75% or more). Weingarten, who considered this entity distinct from that of Loeffler's syndrome, pointed out that these patients are more debilitated, there is often splenomegaly, and, although the etiology is unknown, there is a dramatic response to treatment with arsenicals. Apley and Grant[3], on the other hand, showed that there are many similarities and gradations between Loeffler's syndrome and tropical eosinophilia and that the distinction between them is not definite. After a complete comparison of the two conditions Wise[139] concluded that they are two clinically similar syndromes which require diagnostic differentiation because of the morbidity and mortality in the one case and the transiency in the other, and as a result of the differentiation the seriously crippling disease may be treated with absolute specificity.

In 1947 Perlingiero and György[91] described a syndrome of chronic eosinophilia and eosinophilic granulomatous lesions in the liver associated with fever, leukocytosis, hyperglobulinemia, and pulmonary changes. Biopsy of the enlarged liver showed lesions characterized by focal necrosis, with infiltration of neutrophils and eosinophils. The pulmonary infiltrations were transient and after the patient vomited a single adult male *Ascaris*, he improved remarkably with reversion of the granulomas of the liver. In 1949 Zuelzer and Apt[145] described 8 cases of eosinophilia of blood and bone marrow, leukocytosis, and hyperglobulinemia. There were no clear-cut criteria for a clinical syndrome embracing the entire series, but among the clinical manifestations were asthma, urticaria, coryza, encephalopathy, convulsions, hepatomegaly, and pulmonary infiltration. A search for *Ascaris* was made but none was found and results of skin tests for *Ascaris* and other common parasites were negative. In 1950 Mercer and associates[82] reported an interesting case of larval ascariasis as a cause of chronic eosinophilia with visceral manifestations. This case, with the exception of the hepatomegaly, bears a striking resemblance to the described cases of tropical eosinophilia and "chronic" Loeffler's syndrome. The patient, a 2-year-old white girl who had been sick for 5 months prior to admission, was admitted with gross distention of the abdomen and enlarged liver and spleen. The white blood count was 38,000 per c.mm. with 62% eosinophils. Repeated fecal examinations yielded negative results. Aspiration of the bone marrow showed severe eosinophilic hyperplasia. Infiltration of the right upper lobe and increased hilar markings with an area of miliary infiltration at the base of the right lung were noted in the roentgenogram. Liver biopsy revealed scattered granulomas, the lesions being similar to those reported by Perlingiero and György[91] and Zuelzer and Apt [145]. Four larvae were

identified within the substance of the liver as migrating *Ascaris lumbricoides*. The child passed a 6-inch worm identified as a male *Ascaris lumbricoides*. Three separate courses of hexylresorcinol were followed each time by administration of a purgative and an enema, after which examination of all stools revealed neither worms nor ova.

Among the agents implicated as causes of Loeffler's syndrome are: *Ascaris lumbricoides*[135], *Fasciola hepatica*[66], *Ancylostoma braziliense*[142], *Trichina*[114], *Brucella abortus*[27], *Mycobacterium tuberculosis*[67], privet[28] and ragweed pollen[2], coccidioidomycosis[25, 136], *Endamoeba histolytica*[55,103,121], *Necator americanus*[142], *Strongyloides stercoralis*[8], and sulfonamides[26]. Mite infestation (*acariasis*) has been implicated as the cause of tropical eosinophilia[116]. This organism has also been reported as occurring in 8 cases of transient pulmonary infiltration associated with eosinophilia and minimal symptomatology. This wide variety of apparent etiologic agents would suggest that all these conditions represent a pattern of response to antigenic stimuli. A gradation of cases from mild to severe could easily be assembled. Certain of them would be of the *forme fruste* type, whereas others would take the course of those patients described by Perlingiero and György[91], Zuelzer and Apt[145], and Mercer and coauthors[82]. Though there may be clinical utility in separating these various syndromes, it appears to the authors that all represent aspects of the same underlying mechanism.*

Tuberculosis. The interrelationship between pulmonary tuberculosis and bronchial asthma remains controversial. Some authors consider the diseases mutually exclusive; others believe that asthma and tuberculosis may occur in the same person coincidentally, and finally there are those who think that asthma may predispose to tuberculosis or by contrast that tuberculosis may favorably influence the course of bronchial asthma. An excellent study of Tocker and Davidson[125] has done much to settle these points. In complete refutation of the first premise, they reported an incidence of 3.1% of asthma among 386 tuberculous patients at Sea View Hospital, a figure which is much higher than that of the general population. No evidence was uncovered by them to support the view that tuberculosis predisposes to asthma. They did report improvement in asthmatic symptoms with the onset of tuberculosis, and conversely, with improvement or healing of the tuberculous lesions, the asthma tended to become more acute. Their study confirmed the views of Hamam[45] and of Lueg[73] that asthma exerts an unfavorable course on tuberculosis because, as they pointed out, the asthmatic paroxysm, with its intense cough and increased secretion, facilitates bronchogenic spread from an active caseopneumonic focus. Wheezing dyspnea in tuberculosis may be the result of tracheobronchitis, pressure of nodes, mediastinal shift, and the like, any one of which might result in the incorrect diagnosis of bronchial asthma.

Pulmonary Interstitial Emphysema, Mediastinal Emphysema, Subcutaneous Emphysema, and Spontaneous Pneumothorax. Contrary to what might be expected, the presence of air in the extrapulmonary spaces is an un-

* Editor's note: That tropical eosinophilia and Loeffler's syndrome are not identical is supported by the observation that ACTH cures the latter promptly, but in the former produces only a temporary improvement in fever and in total leukocyte count, the percentage of eosinophils remaining unchanged. When ACTH is stopped, the clinic picture recurs promptly in its initial form. Arsenic then effects the usual prompt cure.

usual complication of bronchial asthma. A search of the literature in 1944[29] revealed only 20 recorded cases of spontaneous pneumothorax complicating asthma; only 2 of these had been proved at autopsy, to which a third case was added. In 1945 Schwartz[107] analyzed the 25 previously recorded cases of spontaneous, mediastinal, and subcutaneous emphysema complicating asthma, and added one of his own. Since then, additional cases have been reported[14,17,34,43,65,81,92,113,140].

It has been pointed out that the normal pleura does not rupture until the intrapulmonary pressure exceeds 200 mm. of mercury, a tension which cannot be produced by the severest paroxysm of coughing[133]. It might seem that the thinned, weakened pleura of emphysematous lungs[143] might be much more susceptible to rupture, but this too was found to be an unusual event[59], the increasing intrapleural pressure in emphysema perhaps representing a protective and compensatory state[15].

The Macklins[77] suggested a most ingenious explanation for the manner of escape of air into the extrapulmonary spaces, which has been widely accepted. According to them, pulmonary interstitial emphysema results from rupture of *marginal* alveoli, that is, those whose bases rest against structures such as bronchi, bronchioles, blood vessels, connective tissue or pleura, in contrast to *partitional* alveoli whose bases rest against other alveoli with which there is intercommunication by means of pores. There are 2 mechanisms operating to allow the escape of air from marginal alveoli: factor A, overexpansion of alveoli without a corresponding widening of the lumen of the blood vessels which they border, resulting in formation of a pressure gradient; and factor B, reduction in caliber of the pulmonary blood vessels without a corresponding decrease in size of the alveoli, again resulting in a pressure gradient which may cause leakage of air. The escaping air makes its way along blood vessel sheaths and peribronchial connective tissues where its splinting action reduces the effective ventilation of the involved segment of lung (airlock). Dissecting its way into the mediastinum, it may cause circulatory embarrassment due to pressure upon the heart and mediastinal vessels (airblock). From the mediastinum, the air may escape into the neck and subcutaneous tissues, or downward along the aorta into the retroperitoneal space. Dramatic symptomatic relief has been described following the appearance of air in the neck and subcutaneous tissues, such escape having a decompression effect upon the mediastinal structures[43]. Rupture may occur into a pleural cavity (pneumothorax) or into the abdominal cavity (pneumoperitoneum).

Prior to the work of the Macklins, the usual explanation offered was that of the "valve vesicle", the ball-valve action making possible the development of high pressures within emphysematous blebs which subsequently ruptured or it was explained on the basis of tearing of adhesions attached to such blebs. In fact, such torn blebs have been described at autopsy[29,59].

The symptoms of the escape of air into extrapulmonary structures vary considerably; it may be a completely occult phenomenon, or there may be an acute onset of thoracic pain, cyanosis, shock, and collapse[77]. The symptoms may suggest pericarditis, myocardial infarction, pulmonary infarction, pneumonitis, peritonitis, or an acute abdominal catastrophe.

The findings depend upon the amount and position of the ectopic air. If air is in the mediastinum, Hamman's sign[46] (a peculiar crunching sound synchronous with the heart beat) may

be present. Roentgenologic observations of pneumomediastinum are a widened mediastinal shadow enclosed by two thin radiolucent lines in anteroposterior projection and the presence of visible air behind the sternum on lateral view of the chest. If air escapes into the subcutaneous tissues, swelling and crepitation may first appear in the region of the suprasternal notch, spreading by tissue planes over much of the body surface, or evidences of pneumothorax or pneumoperitoneum may be present.

Treatment of these conditions is conservative, the only indication for decompression being a tension pneumothorax[29]. Under such management the prognosis is usually good, the ectopic air being resorbed in 10 to 14 days; breathing 100% oxygen aids in resorption of nitrogen from the gaseous deposits[33].

Obstructive Emphysema. According to Rubin[105], bronchial asthma is one of the major causes of obstructive pulmonary emphysema, which Wilson and Bradford[137] believed is probably the commonest chronic respiratory disease encountered in male adults. Rackemann[101] considered emphysema always to be present in bronchial asthma, although usually as a temporary, reversible process.

Emphysema is characterized by pronounced distention of the alveoli and dilatation of the alveolar ducts and terminal bronchioles, owing to increased resistance to the passage of air, particularly in expiration. The elastic fibers supporting the alveolar structures are destroyed, so that the lungs are inelastic and tend to remain distended in the position of inspiration. With the loss of alveolar walls and septa there is concomitant reduction in the pulmonary capillary bed, with degenerative and sclerotic changes in the pulmonary vessels.

Under these circumstances the expiratory phase of respiration, rather than being a passive process, becomes an active one requiring the use of accessory muscles of respiration, with the development of positive intrapleural pressures. Baldwin, Cournand, and Richards[6] classified chronic emphysema according to whether *ventilatory impairment* is present alone or in association with *respiratory insufficiency*. Ventilatory impairment is manifested by enlargement of the thorax, use of accessory muscles in breathing, dyspnea, and increase in total pulmonary capacity, particularly in the residual air fraction. In moderately severe cases the impairment of ventilatory function and resultant maldistribution of intrapulmonary air may be compensated, under ordinary circumstances, by hyperventilation. When this is no longer possible, respiratory insufficiency appears, with cyanosis, weakness, mental confusion, arterial hypoxia, carbon dioxide retention, acidosis, polycythemia, and finally chronic heart failure and death.

The emphysematous patient is dyspneic, with rounded, hyper-resonant chest and with labored respirations, although the chest and diaphragm are relatively fixed in the inspiratory position. Breath sounds are diminished, with prolongation of the expiratory phase. Cyanosis may be present; clubbing of the fingers is uncommon. Reduction in vital capacity may not be striking, but the maximal breathing capacity is greatly reduced. In cases in which complete pulmonary function studies cannot be made, Wilson and Bradford[137] have pointed out the value of determining the time required for complete expiration, prolongation of which is one of the earliest and most constant signs in emphysema. The time required to expire completely into a vital capacity machine is measured

with a stop watch. Usually a complete, forced expiration can be accomplished in less than five seconds; appreciably longer times are indicative of difficulty in emptying the lungs.

Consideration of the asthmatic paroxysm and the emphysematous state reveals many similarities in pathology, pathologic physiology, and physical signs and symptoms (except that wheezing is not nearly so prominent in emphysema). Of course, the factors are constant and persistent in emphysema but episodic in asthma.

Since an element of bronchiolar spasm is almost always present in emphysema, there are certain therapeutic measures common to it and to asthma. Although a complete discussion of therapy in emphysema is not indicated here, the rational use of bronchodilators and expectorants should be emphasized, since they are often neglected. Other therapeutic measures include rest (the emphysematous patient is often most comfortable lying *flat* in bed, possibly with the foot of the bed slightly elevated), the preventive and active treatment of respiratory infections, weight reduction and postural drainage when indicated, breathing exercises, use of an abdominal binder, and judicious use of oxygen. Oxygen is extremely beneficial in patients with emphysema who have respiratory insufficiency. However, the breathing of oxygen in high concentration for even a short time may result in severe carbon dioxide retention and respiratory depression[6]; therefore, oxygen therapy should be carefully controlled, and best results may be achieved by its intermittent use in moderately low concentration.

Cardiac Complications. Although the general impression is that cardiac complications of asthma are unusual[101], right ventricular hypertrophy and dilatation are found in most cases at autopsy[20,48,56,61,74,98], so that heart disease must be frequently associated with the prolonged, severe asthmatic state[72, 106]. It has been suggested that heart disease is indeed more common in asthma than is generally recognized. Cardiac failure is particularly apt to occur in asthmatic persons with preexisting heart disease. In such instances the greatly increased cardiac work, the anoxemia resulting from the inadequate respiratory exchange, and the reduced coronary flow due to increased pressures within the right ventricle and atrium interfering with drainage from the Thebesian vessels and coronary sinus could be expected to overtax a previously weakened myocardium to the point of failure[76]. Also, the increased intrathoracic pressure brought about by the prolonged and forceful expiratory movements are transmitted to the right ventricle by the pulmonary arteries and serve to diminish the return of systemic blood to the heart. In such instances the asthmatic attack represents a grave additional stress for the already abnormal heart, the nature and extent of the underlying heart disease being of primary importance.

Pulmonary heart disease (cor pulmonale) is the type of heart disease characteristic of protracted bronchial asthma. Studies which might lead to the diagnosis of acute or subacute cor pulmonale (measurement of pressures within the right auricle and ventricle and pulmonary artery of a previously normal heart during an early asthmatic paroxysm) have not been reported. However, recently reported were studies on a patient with bronchial asthma of 5 years' duration in which elevated right ventricular systolic and diastolic pressures (apparently measured when the patient was free of asthma) were interpreted as representing an early stage of chronic cor pulmonale[38].

Many suggestions have been made as to the mechanisms operating in emphysema and asthma to produce changes in the right side of the heart[117]. Recent cardiopulmonary function studies[6,32] in patients with chronic pulmonary emphysema and various stages of pulmonary heart disease have done much to elucidate the developmental history of the process. Anatomic reduction in the pulmonary vascular bed is one major operating factor, and its severity depends upon the type of underlying pulmonary disease, especially the degree of diffuse fibrosis. Hypoxia is the other major etiologic factor, since it exerts profound effects upon the hemodynamics of the pulmonary circulation, causing increases in the pulmonary artery pressure, cardiac output, blood volume, and hematocrit. That abnormal elevations of these values in the right ventricular failure of early stages of chronic cor pulmonale may be reversed by adequate therapy has been demonstrated[32]. Factors of less importance which may also operate to produce right ventricular hypertrophy include secondary pulmonary arteriolarsclerosis, possible shunts existing between the pulmonary and systemic circulations, overfilling of the heart, inspiratory pull on the pericardium, and secondary polycythemia[117].

Further knowledge of the condition has been derived largely from pathologic studies. According to Spain and Handler[117], the diagnosis of chronic cor pulmonale can be made at autopsy if hypertrophy is found predominantly of the right ventricle, the right ventricular wall measuring over 5 mm. in thickness, after, of course, all other possible etiologic factors of heart disease have been excluded clinically as well as pathologically. Of 12 autopsied cases of bronchial asthma reported by Schiller, Colmes and Davis[106], 4 were observed to have predominant hypertrophy of the right ventricle. Actually, it is difficult to determine the role played by asthma in the genesis of chronic cor pulmonale because emphysema is always present. When 4 reported series[109,115,117,119] of autopsied cases of cor pulmonale totaling 167 cases were combined, emphysema was found to be present in 104 (62.3%), and bronchial asthma in only 14 (8.3%). In 2 of these series[109,119] asthma was not listed at all, so that such data may tend to underemphasize the role of asthma in cor pulmonale; this is understandable, since the pathologic alterations of emphysema are easily recognizable, whereas bronchial asthma may be a purely clinical or historical diagnosis which may be lost when pathologic material is reported.

Clinically, the appearance of pulmonary heart disease is difficult to recognize, because many of the symptoms, such as dyspnea, cough, and cyanosis, are essentially those of the underlying bronchial asthma and emphysema. As pointed out by Sodeman[115] and Gelfand[38], aggravation of the dyspnea and cyanosis may precede the signs of frank right-sided failure: the distended cervical veins, hepatomegaly, and dependent edema.

Physical examination of the heart is also difficult because of the underlying pulmonary state. Sodeman[115] stressed 2 early findings, often overlooked, which may prove helpful: accentuation of the pulmonary second sound (suggestive of hypertension in the pulmonary circuit), and the precordial systolic retraction wave (suggestive of right ventricular hypertrophy).

Determination of circulation times may also be of diagnostic value. The circulation time is ordinarily normal or accelerated in asthma or emphysema[54]; the output of the heart even in cardiac failure tends to be high, since the ox-

ygen-carrying power of the blood is diminished, a high cardiac output being necessary for maintenance of oxygenation of the tissues[79]. However, when frank failure of the right side of the heart occurs (decompensated stage of cor pulmonale), the arm-to-lung time is increased without increase of the lung-to-tongue time, as determined from the ether and decholin circulation times[54].

Electrocardiographic studies may be of considerable assistance in determining the presence of right ventricular hypertrophy of cor pulmonale. Suggestive changes include: (1) high, peaked P waves and prominent auricular T waves in leads II, III and V_F; (2) negative P waves in V_L; (3) rightward deviation and decreased value of $\bar{A}_{QRS}$; (4) small ventricular gradient (frequently deviated); (5) signs of clockwise rotation (S_1Q_3 pattern) and backward position of the apex (S_1 S_2 and S_3; S_1 and S_2 with rightward deviation of $\bar{A}_{QRS}$); (6) diphasic (of $- +$ type) or negative T waves in leads III, II and V_F; (7) small R waves in the precordial leads; (8) deep S waves in the left precordial leads; (9) diphasic ($+ -$ type) or negative P waves in the right precordial leads; (10) negative T waves in the right precordial leads; (11) incomplete or complete right bundle branch block[60,75,89,144]. It should be emphasized that none of these electrocardiographic signs is diagnostic; actually all are probably the result of changes in position of the heart within the chest and of changes in conduction of the electrical impulse in the emphysematous chest. However, such studies are helpful in arriving at a diagnosis, and, in fact, abnormal electrocardiographic findings may first indicate to the clinician the presence of pulmonary heart disease.

Enlargement of the right side of the heart may be demonstrated roentgenographically. Prominence of the right border due to right auricular and ventricular enlargement, convexity in the region of the pulmonary conus, and readily visible pulmonary arterial branches in the hilar regions are the typical findings in the postero-anterior roentgenogram. However, it is often necessary to resort to fluoroscopy or oblique views, the enlarged pulmonary conus (outflow tract) being best delineated in the right anterior oblique position, the enlarged right auricular segment and prolonged right ventricular inflow tract being visible in the left oblique position[108].

Therapeutic measures directed toward the heart for congestive failure due to chronic cor pulmonale are the same as when due to other conditions and include digitalization, sodium restriction, diuresis, rest, and intermittent administration of oxygen[79,134]. Venesection is of little or no value during early failure, when arterial oxygen unsaturation and high cardiac output are present[79], but may be of value later when the cardiac output is reduced to normal, in order to correct the hypervolemia and polycythemia[32]. McMichael[79], as well as others, has noted that administration of digitalis often does not result in the degree of improvement expected. Indeed, in many cases once frank decompensation has appeared, nothing seems to avail, the patient deteriorating rapidly and dying from a nonrecurrent form of heart failure in a short time[122]. Such cases serve to emphasize the importance of early diagnosis, with adequate treatment of the pulmonary condition. Adequate therapy consists essentially in administration of antibiotics to control pulmonary infections, aggressive management of the asthmatic attacks with bronchodilators by aerosol as well as other routes of administration to relieve bronchiolar obstruction and re-

duce bronchial secretions, and appropriate hyposensitization procedures to lessen the severity and frequency of the asthmatic attacks.

LARYNGEAL VERTIGO. About 75 years ago Charcot[16] described a syndrome characterized by coughing and unconsciousness, which he called laryngeal vertigo (laryngeal epilepsy, tussive syncope, cough with unconsciousness). One of Charcot's patients had asthma and the authors also have seen it in asthmatic patients. The condition typically affects robust middle-aged men of pyknic frame. Men are affected 19 times more often than women. The age at onset is classically between 30 and 60 years. The cough is due to a variety of underlying diseases, the commonest being chronic bronchitis and emphysema. The degree of coughing antecedent to the syncope is variable, though usually it is severe. In a given individual coughing does not always precipitate attacks, the frequency varying greatly. Most patients describe a tickling in the throat prior to the coughing. In one case unconsciousness followed sneezing or blowing the nose[40], and in the case of Lillie and Thornhill[69] attacks could be induced by direct stimulation of Arnold's nerve. Voluntary coughing is usually incapable of inducing syncope. True vertigo is generally not present. The alteration of consciousness may be and usually is complete. During the period of syncope, twitching of one or more limbs or even convulsions of the entire body may be apparent. It is not unusual for patients to injure themselves in falling. Slight mental confusion after the episode is common but by no means invariable. Precipitating factors in most instances are not discernible. The patient is suddenly seized with a desire to cough. In an impressive percentage of reported cases episodes occurred at meal times; odors particularly from tobacco smoke were also frequently capable of inducing the paroxysm.

If the condition is thought of, the diagnosis is simple. Since this is a symptom, the cause of the cough must be established. Among diseases to be excluded are epilepsy, narcolepsy, carotid sinus syndrome, and laryngeal crises of tabes. The prognosis depends on the underlying cause, but patients should be warned that accidents resulting from attacks while driving cars make them guilty of antecedent negligence in most jurisdictions.

PREGNANCY. The effect of pregnancy on asthma is extremely variable. The asthma may improve considerably or even disappear, or it may be aggravated by the pregnancy. Sex of the fetus at times appears to influence the asthma. Finally, the asthma may exert its influence on the pregnancy. These problems were reviewed in 1946[23]. Certain of these observations may be repeated. The inconstant relationship between asthma and pregnancy is seen in the time of onset of the attacks. The asthma may be worse only during the first months of pregnancy, after which there is improvement or remission. Again, attacks may become worse only in the latter months of pregnancy or more severe attacks may start early and become progressively worse. These varied interrelationships are difficult to explain because of the complexity of factors occurring in pregnancy and exercising an influence. Aggravation of the asthma has been blamed on mechanical factors, such as diminution in the thoracic space with consequent reduction in vital capacity. This may play a role in the latter half of pregnancy but many of the most severe instances occur in the first trimester. In other cases the asthma improves at precisely the time when the mechanical impediment appears to be greatest.

The risk to life is greater for the fetus than for the mother. In general, the prognosis for the mother is favorable; thus, none of the asthmatic mothers in the series of 60 pregnancies collected at Charity Hospital in New Orleans died, and death occurred in only 4 of the cases collected from the literature. The fetal mortality in the Charity Hospital series was 11% (5 spontaneous abortions and 2 premature deliveries). According to the Metropolitan Life Insurance Company[120], the fetal mortality rate per thousand live births is 32. European physicians are not loathe to interrupt pregnancy in order to relieve the mother. Everyone agrees that emptying of the uterus always relieves the severe dyspnea, and even though cough may persist for a time, its character changes and expectoration decreases. No instance could be found in the literature in which the asthma became worse after delivery. American thought appears to be more conservative, for the Charity Hospital experience included no therapeutic abortions and but 1 induction of labor.

Constitutional reactions characterized by cramping of the uterus, scanty menstrual flow, or emptying of the pregnant uterus have been reported during the course of desensitization. No more than 3 instances of abortion induced in this fashion could be found in the literature. It is believed, therefore, that the danger of interrupting pregnancy during treatment is extremely slight and far less than that caused by untreated bronchial asthma.

Postoperative Complications. Since persons with asthma are not immune to diseases requiring major operations, it is important to know the incidence of postoperative pulmonary complications and the apparent mortality risk in such patients. Gaarde and coworkers[36] studied this problem in 189 consecutive patients with allergic asthma or asthmatic bronchitis in whom major operations were performed at the Mayo Clinic. In only 25 of the these did some form of postoperative pulmonary complication develop. They pointed out that for the general population, the incidence of pulmonary complications after operations in the upper part of the abdomen is approximately double that after operations on the lower part of the abdomen, whereas in the group of asthmatic patients this ratio was approximately 3 to 1. In the entire group of 189 patients only 4 deaths occurred, a case fatality rate of 2.1%. All their patients received special preoperative and postoperative care.

Increase in intra-abdominal pressure is well known to occur in coughing. It might be anticipated that the chronic cough of certain asthmatic persons might lead to both development and recurrence of various types of hernias. This question was studied by Prickman and Bayrd[94] in a series of 157 patients with asthma and hernias seen at the Mayo Clinic. Hernias were present in 3.4% of this series in contrast to 2.3% of general patients. There were recurrences in 27% of the asthmatic patients with hernias operated on at the Clinic in contrast to recurrences in only 6.4% of all patients with hernias. Of the 157 patients, 109 either were not advised to have the hernias repaired at the time they were seen or were frankly advised not to have them repaired. Not only must care be exercised in choosing which asthmatic person with hernia should be operated on but the time of the operation must also be carefully selected.

Miscellaneous. Bronchogenic carcinoma and other masses may duplicate asthmatic wheezing. In order to re-emphasize the importance of a thorough examination of all asthmatic patients and the necessity of bron-

choscopy in certain of these, Prickman and coworkers[96] reported 3 cases of patients who complained primarily of asthma but who were coincidentally found to have associated primary bronchial malignancy.

Harkavy[49,50], who stressed the role which the blood vessels play in asthma, believed that the vascular endothelium represents the primary site of the allergic reaction. Bronchial asthma, or a history of asthma, occurs often in patients with proved periarteritis nodosa; Rackemann and Greene[102] reported 8 cases of periarteritis with asthma and collected 27 others from the literature. Indeed, it has been suggsted that any asthmatic person with severe eosinophilia and numbness of the extremities should be suspected of having periarteritis nodosa[71].

The interrelations of asthma and sinus disease were recently reviewed by Guerrant and associates[44]. The occurrence of respiratory tetany in asthma has been discussed by Langeron and coworkers[64].

Case reports of other conditions associated with bronchial asthma include transient gastric edema, observed gastroscopically during an asthmatic attack[68]; possible eosinophilic leukemia in a 19-year-old soldier with a long history of asthma (the patient manifesting splenomegaly and a white blood count of 60,000 per c.mm., cells of the eosinophilic series predominating in the peripheral blood and marrow but the observation period being too short for the diagnosis to be established[30]); a fatality considered to exhibit recurrent intracardiac clotting in association with acute bronchial asthma[57]; hereditary hemorrhagic telangiectasia with bronchial asthma[10]; and asthma associated with hemoglobinuria[58].

Status Asthmaticus. The management of this refractory state, one of the commonest complications of bronchial asthma, has been well summarized by McLaughlin and Parkhurst[78]. Cortisone and ACTH have been shown to be capable of interrupting the continued asthmatic state. In an excellent review on ACTH and cortisone in the management of the hypersensitivities Segal and Herschfus[110] devoted particular attention to bronchial asthma. They concluded that improvement frequently may be maintained only a short period; prolonged administration is not feasible; there is some evidence that in relapse the symptoms of hypersensitivity may recur with greater severity than before; repeated stimulation of the hypothalamus–pituitary–adrenal axis may not be desirable; and finally, the extent of undesirable physiologic and toxic effects of ACTH and cortisone in chronic allergic disorders remains to be determined.

Recent reports are appearing to suggest that cortisone and ACTH are capable of worsening various infectious diseases, such as those due to tubercle bacillus, *Streptococcus hemolyticus,* the poliomyelitis virus, and *Treponema pallidum.* Michael, Cummings, and Bloom[54] observed that in rats treated with either substance tubercle bacilli multiplied more rapidly, produced more diffuse disease, and resulted in the death of an animal normally immune to this organism. Similar deleterious effects were noted in mice[51] and guinea pigs[118]. Mogabgab and Thomas[86] reported considerable enhancement of infection due to *Streptococcus hemolyticus* in the tissues and blood of rabbits following injection of cortisone. Shwartzman[112] found an acceleration of the poliomyelitic infection and increase in susceptibility in hamsters after administration of ACTH and cortisone in combination or cortisone alone. In rabbits there was a rebound phenomenon in which syphilomas

reached an unusual size after cortisone withdrawal[126].

Since bronchial asthma is ordinarily classified into extrinsic and intrinsic, depending on whether the exciting cause is external (such as dust, foods, pollens) or internal (bacteria), it would appear that cortisone and ACTH could be used with greatest safety in the extrinsic type. Moreover, many of the cases of status asthmaticus develop in patients with intrinsic bronchial asthma. If signs of infection are present, the offending organism should be cultured, if possible, and by the use of antibiotic sensitivity studies the appropriate therapy should be instituted. Where the use of antibiotics is most indicated in status asthmaticus, the use of cortisone and ACTH has the greatest theoretic dangers. Contrariwise, in those instances in which antibiotic therapy is least useful in status asthmaticus, cortisone and ACTH should be most effective and least dangerous.

Depletion. For several years Rackemann[99,100] has been stressing the need for basing treatment of asthma on the general condition of the patient. It is his well-taken view that in centering attention on the asthma rather than on the patient himself, the physician may easily be responsible for making the treatment worse than the disease. According to Rackemann, depletion may become manifest before the onset of the asthma with the history of an acute illness or operation; emotional disturbances, chronic fatigue, or leading a "hectic" life may initiate asthmatic attacks. Depletion itself may thus be a sufficient cause for asthma. It may also be secondary to chronic severe asthma and as such aggravate the asthma. The presence of asthma may hinder recovery of the general health so that a vicious cycle is established. In one of Rackemann's patients the 17-ketosteroid excretion was only 5.5 mg. as compared with a normal of 15; he related this to the general alarm reaction, pointing out that a severe "shock" will, at least temporarily, make the asthma better. He cited another patient 58 years old with severe asthma, who was emaciated and debilitated, and in whom treatment directed toward improving the general health resulted in almost complete disappearance of the asthma within 2 years. He had had no "allergic treatment", and environmental factors had not been altered.

Related to depletion is disturbance of growth patterns in allergic children. In a comparison of 150 allergic children with normal children using the Wetzel grid (an accepted and accurate method for studying body type and growth in children), Cohen and Abram[18] concluded that active allergy is a common cause of growth failure and control of active allergy may be accompanied by a corresponding regain in growth, provided adequate diet is available.

Death. Despite the high morbidity of asthma the case fatality rate is extremely low, even in status asthmaticus. Though many patients die with bronchial asthma, few die *from* it. Bronchial asthma may cause death at any age, and as early as 1911 an autopsied case of a child 2 years old was reported[52]. Other fatal cases in infants were recorded by Thieme and Sheldon[124] and by Pratt[93]. From the 2nd through the 20th years deaths from bronchial asthma are extremely rare, only about 8 such cases having been reported. The majority of recorded deaths occurred after the 3rd decade. As Peterson[92] has rightly stated, because asthma is so rarely fatal, particularly in the younger patients, a false sense of security leading to lethargic treatment is undoubtedly often present, as contrasted to the

care awarded the more obviously dangerous medical illnesses.

Deaths in asthmatic persons may be the result of diagnostic procedures (skin tests), therapeutic procedures (specific antigenic or nonspecific drug therapy), or the disease itself. Blanton and Sutphin[9] reported the 11th case of death from skin testing to be recorded in the literature. Informal conversation with physicians, however, has disclosed at least an additional dozen unpublished instances. Deaths have occurred after an intracutaneous test with LePage glue[21], egg white[63], buckwheat[63], egg[5], horse serum[30,35], silk, wool, and kapok[127]. Deaths in asthmatic individuals have also been reported after the use of unspecified antigens[123]. In the case reported by Blanton and Sutphin[9], 56 intracutaneous tests had been made prior to death. Since the majority of the deaths from testing of asthmatic persons has followed the intracutaneous application of antigen, most allergists advocate that every intracutaneous test should be preceded by the less sensitive scratch test. Death is said to be caused from asphyxia resulting from bronchial obstruction consequent to edema of the walls of the small bronchi, spasm of smooth muscles, and mucous plugging of the lumens of the bronchi. Study of the gross and microscopic findings of Blanton and Sutphin's patient revealed no direct evidence of spasm or extensive edema, unless one is willing to accept the infolding of the mucous membranes as indicating smooth muscle contraction of the bronchial walls; mucus in the lumens of the small bronchi was impressive but aside from this the cause of the obstruction remained a matter of conjecture.

Pertinent to this discussion is the recent work of Moss, Beiler, and Martin[88], which indicates that histidine decarboxylase, present in animal tissues, is capable of forming histamine from histidine. Their *in vitro* and *in vivo* tests show the inhibitory effects of vitamin P (d-catechin) against this enzyme. In their study 14 guinea pigs were sensitized; half of these received 2 mg. of d-catechin, an aglycone flavenoid, and the remaining served as controls. At the end of the experiment each animal received an intracardial injection of antigen. The animals receiving the d-catechin exhibited no reaction, whereas the controls had typical anaphylactic reactions, dying of asphyxia within 5 minutes. Four additional pigs which had received daily doses of d-catechin for 1 week were injected intracardially with 0.1 mg. of histamine diphosphate. These animals died several minutes later with typical shock symptoms. At autopsy no significant differences between the 2 groups of dead animals could be detected. The predominating characteristic in both groups of animals was constriction of the bronchiolar muscles. Each animal showed varying degrees of pulmonary edema and hyperemia. They concluded that the flavenoid protected against anaphylactic reactions but not against histamine shock. It appears reasonable to believe this protective activity might be attributed to actual inhibition of histidine decarboxylase. This reaction would tend to prevent the formation of histamine, which is an important factor in the anaphylactic syndrome. The extreme rapidity with which death ensues in human anaphylaxis from skin tests or antigen therapy may be supposed, therefore, to be on the basis of enhanced activity of undesirable enzymatic action or, contrariwise, from impaired or nullified desirable (that is, protective) enzymatic action.

Deaths have been attributed to the use of morphine, aminophylline, and procaine in the treatment of bronchial

asthma. Most allergists condemn the use of morphine because such a high percentage of the deaths reported during asthmatic attacks has been in patients who had received this drug. All admit that morphine frequently gives great relief when many other measures have failed, but the risk of giving morphine far outweighs its usefulness in the management of the patient with allergic bronchial asthma. A continually depressant action is exerted on the respiratory center by morphine, the effect being proportional to the dose. At first the respiratory rate is diminished, but the tidal volume may increase enough actually to raise the minute volume of respiration. Soon, however, both depth and rate of respiration are diminished. The cough reflex is abolished and the lumen of the bronchi may be narrowed. Physiologically, the drug is, therefore, contraindicated, since it may both increase bronchial constriction and prevent expectoration of exudate from the bronchi[62]. Any beneficial effects probably stem from relief of apprehension which at times approaches mania. Mental relaxation can be secured almost as well with far less dangerous forms of sedation, such as meperidine. However, one of the outstanding authorities[22] in the field does not agree: "There are many who believe that opium and its derivatives should never be used in asthma. I do not concur. Such sedation must be given carefully and in doses to control cough and allay distress but not in amounts sufficient either to slow respiration appreciably, to stop cough, or do more than produce the mildest relaxation. If vomiting occurs, so much the better." Perhaps the advent of ACTH and cortisone will settle the controversy by rendering the use of sedatives in severe asthma unnecessary.

By contrast with morphine, aminophylline has enjoyed wide use in the treatment of bronchial asthma. However, some deaths have apparently followed its intravenous administration. Thus, Merrill[83] reported cessation of respiration and heart sounds within 30 seconds after the "slow" intravenous administration of 0.25 gm. of aminophylline dissolved in 10 cc. of 10% solution of dextrose to an asthmatic patient. Similarly, Bresnick, Woodward, and Sageman[11] described 3 cases of sudden death following the slow intravenous use of aminophylline in patients who were not moribund at the beginning of the injection. The total dose administered did not seem important, the fatal dose varying from 0.1 gm. to 0.36 gm. It has been repeatedly observed that too rapid injection of aminophylline intravenously may evoke toxic symptoms referable to the central nervous system including hyperpnea, vertigo, and faintness.

An aminophylline-containing preparation (tedral), when accidentally consumed, caused a fatality in an asthmatic child, aged 2 years[37]. The child ingested a maximum of 0.2 gm. ephedrine, 1.0 gm. theophylline, and 0.065 gm. phenobarbital, which was considered to be a sublethal dose. In order to determine the possible synergism of these drugs Gardner and coworkers[37] studied a series of 510 mice. The toxicity of ephedrine was nearly tripled by the concomitant action of aminophylline in this species. The toxicity of aminophylline was nearly doubled by the concomitant action of moderate amounts of ephedrine. Mixtures of these drugs containing relatively high proportions of aminophylline are extremely synergistic. They concluded that theophylline in high dosage may be potentially more dangerous than is commonly thought. Despite these deaths, aminophylline remains a use-

ful drug in the management of the attack of bronchial asthma.

Death of a patient with severe status asthmaticus treated successively with intravenous injection first of procaine and then of sodium amytal was reported by Gelfand, Mufson, and Richman[39]. The patient had typical symptoms of procaine poisoning: tremor, excitement, violent clonic convulsions, cyanosis, cardiac irregularity, and paralysis of respirations. An excellent paper describing interrelationships of local anesthetics and antihistaminics is that of Burn[13].

Death results in asthma when the bronchial obstruction is not reversible. The obstruction is caused by bronchial spasm, edema of the bronchial mucosa and submucosa, and accumulation of large amounts of thick tenacious inspissated mucus.

Perhaps the observations of extreme bronchospasm in guinea pigs' anaphylaxis have overemphasized the role of contraction of bronchial musculature in human asthma. Burch[12] pointed out, nevertheless, that reflex phenomena initiated in the upper respiratory tract by the allergen may be responsible for some muscular spasm in the bronchioles. He added that there is a great tendency to consider psychogenic states, commonly associated with asthma, as contributing to these reflexes and the bronchiolar spasm. He stated further that the spasm may be initiated by reflexes stimulated by inspiration of cold moist air and by dermovasoconstrictor reflexes from contact with cold moist air. The mucosal and submucosal edema may be of allergic or inflammatory origin. Other factors must be operative, for Barach[7] demonstrated that during obstructive dyspnea, as in asthma, there develops a high negative intrapulmonary pressure which makes possible entrance of air past the point of constriction. The direct suction action during inspiration on the pulmonary capillaries may result in transudation of serum into the alveolar cells as well as production of mucus from the intrathoracic bronchial mucosa. Furthermore, those patients in whom status asthmaticus is most likely to develop have had the disease for some time. Pathologic alterations in the bronchial wall (widening of the basement membrane, infiltration with eosinophils, widening of the submucosa, hypertrophy of the musculature, and presence of degenerative mucous glands) have been demonstrated repeatedly in patients dying from asthma. These alterations, although not pathognomonic of bronchial asthma, are considered by Alexander[1] to be highly suggestive. The loss of ciliary form and function which accompanies these changes may be an important factor (as suggested by Hilding[53]) in death from asthma. Hilding described this change as consisting of goblet or goblet-like cells in place of the normal columnar ciliated cells. This, he thought, is apparently a true metamorphosis in the course of which the ciliary mechanism is lost and the typical mucinous viscid secretion accumulates in the air passages. In normal persons this secretion is readily carried out by ciliary action. The amount of secretion is increased, according to Hilding[53], because the one-time ciliated cells are secreting as well as the glands. The difficulty of removal of the secretions is increased because the mucus remains adherent over large areas within the cells which produce it, thus anchoring the mass to the wall.

Through these varied mechanisms there results a stasis of air in the alveoli with more complete removal of oxygen and accumulation of carbon dioxide; this produces hypoxic hypoxia and acidosis. Van Liere[128] stated that in the extreme hypoxia of high alti-

tudes there is an initial alkalosis rather than acidosis because the unobstructed airways permit the development of acapnia following hyperventilation. In either case as death approaches, the respiratory center fails.

As Selye[111] has shown, as an essentially allergic disease asthma must also be considered as primarily a disease of adaptation. Stress[111], like ACTH[104], at times ameliorates and at other times worsens asthma. Selye further states that the anti-asthmatic effect of the gluco-corticoids and of adrenergic substances suggests that endogenous discharge of adrenal hormones may be a normal defense reaction against this abnormal or allergic response to certain agents. An inadequacy of this response may well play a role in the pathogenesis of asthma.

Giragossintz and Sundstroem[42], who worked with rats under hypoxic conditions for an extended period of time, found cellular necrosis and hemorrhage of the adrenal. They believed that the functional alterations observed were identical with those seen in corticoadrenal insufficiency in adrenalectomized animals. When cortical hormones were administered to these animals, the effects were ameliorated. Armstrong and Heim[4] noted similar results after subjecting rabbits to a simulated atmosphere of 18,000 feet for 4 hours daily. Epinephrine relieves asthma in 2 ways. There is an immediate but transient effect on the bronchi. In many cases the antigenic exposure (dust or pollen, for example) continues and the paroxysm would supervene were it not for the recently described action of epinephrine on the hypothalamus–hypophysis–adrenal cortex circuit. In this fashion adrenal corticoids may be elaborated and forestall the recurrence of the asthma in those instances in which one injection of ephinephrine aborts the attack completely.

Several recent papers have attempted to correlate asthma with the general adaptation syndrome. Thus, Winer, Beakey, and Segal[138] made a clinicopathologic study of bronchial asthma with consideration of its relation to the general adaptation syndrome. In 8 of the group of asthmatic patients who died during an attack mediastinal lymph nodes were available for microscopic examination. In each lymph node examined, the essential architecture was intact; the germinal centers were prominent and showed varying but usually severe degrees of pyknosis and karyorrhexis of lymphocytes and cytophagocytosis of nuclear debris by macrophages. In the one thymus examined there were areas of severe pyknosis and karyorrhexis of thymocytes and phagocytosis by macrophages. The adrenal glands were not remarkable grossly. Sections of 9 adrenals were examined; 2 showed considerable patchy depletions of lipoids, 4 showed slight patchy depletion of lipoids, and 3 were filled with lipoid. As these authors stated, the lymphoid and adrenal changes seen in status asthmaticus are suggestive of the alarm reaction phase of Selye's general adaptation syndrome. It may be pointed out that these changes are also suggestive of the stage of exhaustion. However, Selye repeatedly showed that in the shock phase of the alarm reaction and in the exhaustion stage of the general adaptation syndrome many of the anatomic, physiologic, and chemical changes thus far incompletely studied are similar.

In earlier pathologic studies by MacDonald[74] on 8 asthmatic patients, 5 of whom died during asthmatic paroxysms, the thymus was described as persistent or persistent and hyperplastic; there were generalized hyper-

plasia of the lymph nodes and hypoplasia of the adrenal glands. A group of 7 cases in which death was attributed to asphyxia during status asthmaticus was reported by Thieme and Sheldon[124]. The thymus in 5 of these was hyperplastic and in 2 atrophic. There was generalized hyperplasia of the lymph nodes in 6 of 7 instances. The adrenals were hypoplastic. Had these investigations been made in the light of the general adaptation syndrome, less apparent inconsistency between these observations and those of Winer, Beaky, and Segal[138] might have been shown. Despite the brilliant speculations of Selye[111], the exact role that the general adaptation syndrome plays in death from bronchial asthma remains uncertain.

REFERENCES

(1) **Alexander, H. C.:** in discussion of **Michael, P. P.,** and **Rowe, A. H.:** J. Allergy, **6,** 150, 1935. (2) **Alpher, I. M.:** Ibid., **18,** 39, 1947. (3) **Apley, J.,** and **Grant, C. H.:** Lancet, **2,** 308, 1944. (4) **Armstrong, H. G.,** and **Heim, J. G.:** J. Aviation Med., **9,** 45, 1938.

(5) **Baagoe, K. H.:** Ugesk f. Laeger, **90,** 550, 1928. (6) **Baldwin, E. D., Cournand, A.,** and **Richards, D. W., Jr.:** Medicine, 28, 201 1949. (7) **Barach, A. L.:** Physiologic Therapy in Respiratory Diseases, ed. 2, Philadelphia, J. B. Lippincott, 1948. (8) **Berk, J. E.:** J. Am. Med Assn., **127,** 354, 1945. (9) **Blanton, W. B.,** and **Sutphin, A. K.:** Am. J. Med. Sci., **217,** 169, 1949. (10) **Borzone, J. E., Folco, J. A.,** and **Ferraiolo, F.:** Dia méd., **15,** 1207, 1943. (11) **Bresnick, E., Woodard, W. K.,** and **Sageman, C. B.:** J. Am. Med. Assn., **136,** 397, 1948. (12) **Burch, G. E.,** in **Derbes, V. J.,** and **Engelhardt, H.:** Treatment of Bronchial Asthma, Philadelphia, J. B. Lippincott, Co., 1946. (13) **Burn, J. H.:** Brit. Med. J., **2,** 691, 1950.

(14) Case Records of Massachusetts General Hospital (Case No. 32192): New England J. Med., **234,** 639, 1946. (15) **Castex, M. R.,** and **Mazzei, E. S.:** Presse méd., **46,** 529, 1938. (16) **Charcot, J. M.:** cited by **Armstrong, S. T.:** Med. News, **54,** 624, 1889. (17) **Chester, S. W.:** Ann. Allergy, **7,** 783, 1949. (18) **Cohen, M. B.,** and **Abram, L. E.:** J. Allergy, **19,** 165, 1948. (19) **Cole, D. B., Nalls, W. L.,** and **Buis, L. J.:** Virginia M. Monthly, **71,** 505, 1944. (20) **Colton, W. A.,** and **Ziskin, T.:** J. Allergy, **8,** 347, 1937. (21) **Cooke, R. A.:** J. Immunol., **7,** 119, 1922. (22) Idem: Allergy in Theory and Practice, Philadelphia, W. B. Saunders, 1947, 148.

(23) **Derbes, V. J.,** and **Sodeman, W. A.:** Am. J. Med., **1,** 367, 1946. (24) **Diamond, S.,** and **van Loon, E. L.:** J. Am. Med. Assn., **118,** 771, 1942. (25) **Dickson, E. C.:** Ibid., **111,** 1362, 1938.

(26) **Ellis, R. V.,** and **McKinlay, C. A.:** J. Lab. & Clin. Med., **26,** 1427, 1941. (27) **Elsom, K. A.,** and **Ingelfinger, F. J.:** Ann Int. Med., **16,** 995, 1942. (28) **Engel, D.:** Beitr. z. Klin. d. Tuberk., **87,** 239, 1936. (29) **Engelhardt, H. T.,** and **Derbes, V. J.:** Ann. Int. Med., **21,** 711, 1944.

(30) **Fenner, F.:** M. J. Australia, **2,** 7, 1943. (31) **Ferguson, R.:** Canad. Med. Assn. J., 43, 469, 1940. (32) **Ferrer, M. I.:** New York State J. Med., **50,** 1817, 1950. (33) **Fine, J., Hermanson, L.,** and **Frehling, S.:** Ann. Surg., **107,** 1, 1938. (34) **Francis, N.:** Ann. Allergy, **2,** 342, 1944. (35) **Freedman, H. J.:** New England J. Med., **212,** 10, 1935.

(36) **Gaarde, F. W., Prickman, L. F.,** and **Raszkowski, H. J.:** J. Am. Med. Assn., **120,** 431, 1942. (37) **Gardner R. A., Hansen, A. E., Ewing, P. L.,** and **Emerson, G. A.:** Texas State J. Med., **46,** 516, 1950. (38) **Gelfand, M. L.:** Am. J. Med., **10,** 27, 1951. (39) Idem, **Mufson, M. H.,** and **Richman, W. P.:** New York State J. Med., **49,** 2841, 1949. (40) **Getchell, A. C.:** Boston Med. & Surg. J., **135,** 466, 1896. (41) **Ginsburg, M.:** Ann. Allergy, **5,** 488, 1947. (42) **Giragossintz, G.,** and **Sundstroem, E.:** Proc. Soc. Exper. Biol. & Med., **36,** 432, 1937. (43) **Grossman, J. W.,** and **Cramer, O. S.:** Radiology, **52,** 705, 1949. (44) **Guerrant, J. L., McCausland, A.,** and **Swineford, O., Jr.:** J. Allergy, **21,** 187, 1950.

(45) **Hamam, M.:** Beitr z. Klin. d. Turberk., **82,** 619, 1933. (46) **Hamman, L.:** Bull. Johns Hopkins Hosp., **64,** 1, 1939. (47) **Hansen-Pruss, O. C.,** and **Goodman, E. G.:** Ann. Allergy, **2,** 85, 1944. (48) **Harkavy, J.:** J. Allergy, **1,** 136, 1930. (49) Idem: Arch. Int. Med., **67,** 709, 1941. (50) Idem: J. Allergy, **14,** 507, 1943. (51) **Hart, P. D.,** and **Rees, R. J. W.:** Lancet, **2,** 391, 1950. (52) **Heizer, H.:** Cited in Reference No. 56. (53) **Hilding, A. C.:** Ann. Otol., Rhin. & Laryng., **52,** 5, 1943. (54) **Hitzig, W. M.:** Mod. Concepts Cardiovasc. Dis., vol. 16, 1947. (55) **Hoff, A.,** and **Hicks, H. M.:** Am. Rev. Tuberc., **45,** 194, 1942. (56) **Huber, H. L.,** and **Koessler, K. K.:** Arch. Int. Med., **30,** 688, 1922.

(57) **Jessiman, J. B.**: Brit. Med. J., **1**, 557, 1939. (58) **Jones, H. E.**: Glasgow Med. J., **134**, 79, 1940.

(59) **Kjaegaard, H.**: Acta med. Scandinav., **43** (Supp.) 1, 1932; also **80**, 93, 1933. (60) **Kossman, C. E., Berger, A. R., Brumlik, J.,** and **Briller, S. A.**: Am. Heart J., **35**, 309, 1948. (61) **Kountz, W. B., Alexander, H. L.,** and **Prinzmetal, M.**: Ibid., **11**, 163, 1936.

(62) **LaDue, J. S.,** in **Derbes, V. J.,** and **Engelhardt, H.**: Treatment of Bronchial Asthma, Philadelphia, J. B. Lippincott, Co., 1946. (63) **Lamson, R. W.**: J. Am. Med. Assn., **82**, 1091, 1924. (64) **Langeron, L., Michaux, P.,** and **Liefooge, J.**: Ann. d'endocrinol., **9**, 67, 1948. (65) **Larguia, A. E.,** and **Sojo, E. T.**: Arch. argent de pediat., **25**, 35, 1946. (66) **Lavier, G., Bariety, M.,** and **Caroli, J.**: Paris méd., **1**, 434, 1939. (67) **Leitner, S. J.**: Acta med. Scandinav., **97**, 473, 1938. (68) **Lichstein, J.,** and **Benjamin, M.**: Ann. Int. Med., **32**, 967, 1950. (69) **Lillie, H. I.,** and **Thornhill, W. C.**: Ann. Otol., Rhin. & Laryng., **53**, 770, 1944. (70) **Loeffler, W.**: Schwiez. med. Wchnschr., **66**, 1069, 1936. (71) **Logue, R. B.,** and **Mullins, F.**: Ann. Int. Med., **24**, 11, 1946. (72) **Lowance, M. I., Jones, E. C., Matthews, W. B.,** and **Dunstan, E. M.**: South. Med. J., **40**, 508, 1947. (73) **Lueg, W.**: Ztschr. f. klin. Med., **91**, 287, 1921.

(74) **MacDonald, I. G.**: Ann. Int. Med., **6**, 253, 1932. (75) **McGregor, M.**: Brit. Heart J., **12**, 351, 1950. (76) **Mack I., Harris, R.,** and **Katz, L. N.**: Am. Heart J., **39**, 664, 1950. (77) **Macklin, M. T.,** and **Macklin, C. C.**: Medicine, **23**, 281, 1944. (78) **McLaughlin, J. S.,** and **Parkhurst, L. W.**: M. Clin. North America, **33**, 1597, 1949. (79) **McMichael, J.**: Mod. Concepts Cardiovasc. Dis., **19**, 69, 1950. (80) **Mallory, T. B.**: New England J. Med., **237**, 795, 1947. (81) **Mascheroni, H. A., Reussi, C.,** and **Iturbe, R. R.**: Rev. Assoc. méd. argent., **59**, 8, 1945. (82) **Mercer, R. D., Lund, H. Z., Bloomfield, R. A.,** and **Caldwell, F. E.**: Am. J. Dis. Child., **80**, 46, 1950. (83) **Merrill, G. A.**: J. Am. Med. Assn., **123**, 1115, 1943; correction, 124, 250, 1944. (84) **Michael, M., Jr., Cummings, M. M.,** and **Bloom, W. L.**: Proc. Soc. Exper. Biol. & Med., **75**, 613, 1950. (85) **Miller, H., Piness, G., Feingold, B. F.,** and **Friedman, T. B.**: J. Pediat., **7**, 768, 1935. (86) **Mogabgab, W. J.,** and **Thomas, L.**: Report before Central Soc. for Clin. Research, 23 annual meeting Chicago, Nov. 3-4, 1950. (87) **Moll, H. H.**: Lancet, **1**, 12, 1937. (88) **Moss, J. N., Beiler, J. M.,** and **Martin, G. J.**: Science, **112**, 16, 1950. (89) **Myers, G. B., Klein, H. A.,** and **Stofer, B. E.**: Am. Heart J., **35**, 1, 1948.

(90) **Oechsli, W. R.**: J. Thoracic Surg., **5**, 530, 1936.

(91) **Perlingiero, J. G.,** and **György, P.**: Am. J. Dis. Child., **73**, 34, 1947. (92) **Peterson, H.**: J. Allergy, 18, 413, 1947. (93) **Pratt, H. N.**: New England J. Med., 223, 626, 1940. (94) **Prickman, L. E.,** and **Bayrd, E. D.**: Minnesota Med., **28**, 727, 1945. (95) **Prickman, L. F.,** and **Gellbach, P. D.**: Proc. Staff Meet., Mayo Clin., **19**, 384, 1944. (96) **Prickman, L. E., Mavtum, C. K.,** and **Moersch, H. J.**: J. Allergy, **13**, 261, 1942. (97) **Prickman, L. E.,** and **Moersch, H. J.**: M. Clin. North America, **23**, 961, 1939.

(98) **Rackemann, F. M.**: Boston Med. & Surg. J., **194**, 531, 1926. (99) Idem: J. Allergy, 16, 136, 1945. (100) Idem: Trans. Am. Clin. & Climat. Assoc., **58**, 71, 1947. (101) Idem: in **Cecil, R. L.**: Textbook of Medicine, ed. 7, Philadelphia, W. B. Saunders Co., 1947, 537. (102) **Rackemann, F. M.,** and **Greene, J. F.**: Trans. A. Am. Physicians, **54**, 112, 1939. (103) **Randall, T.**: Brit. J. Tuberc., **39**, 37, 1945. (104) **Rose, B., Pare, J. A. P., Pump, K., Stanford, R. L.**: Canad. Med. Assn. J., **62**, 6, 1950. (105) **Rubin, E. H.**: Diseases of the Chest, Philadelphia, W. B. Saunders Co., 1947.

(106) **Schiller, I. W., Colmes, A.,** and **Davis, D.**: New England J. Med., **228**, 113, 1943. (107) **Schwartz, E.**: J. Allergy, **16**, 279, 1945. (108) **Schwedel, J. B.**: Clinical Roentgenology of the Heart, New York, P. B. Hoeber, 1946. (109) **Scott, R. W.,** and **Garvin, C. F.**: Am. Heart J., **22**, 56, 1941. (110) **Segal, M. S.,** and **Herschfus, J. A.**: Ann. Allergy, **8**, 786, 1950. (111) **Selye, H.**: Stress, Montreal, Acta, Inc., 1950. (112) **Shwartzman, G.**: Proc. Soc. Exper. Biol. & Med., **75**, 835, 1950. (113) **Skinner, H. H.**: J. Pediat., **18**, 117, 1941. (114) **Slowey, J. F.**: Ann. Int. Med., **21**, 130, 1944. (115) **Sodeman, W. A.**: Dis. of Chest, **14**, 360, 1948. (116) **Soysa, E.,** and **Jayawardena, M. D. S.**: Brit. Med. J. **1**, 1, 1945. (117) **Spain, D. M.,** and **Handler, B. J.**: Arch. Int. Med., **77**, 37, 1946. (118) **Spain, D. M.,** and **Molomut, N.**: Am. Rev. Tuberc., **62**, 337, 1950. (119) **Spatt, S. D.,** and **Grayzel, D. M.**: Am. J. Med., **5**, 252, 1948. (120) Statist. Bull., Metropolitan Life Insurance Co., **31**, 8, 1950. (121) **Stefano, J.**: Semana med., **2**, 749, 1939. (122) **Strong, G. F.**: Dis. of Chest, **13**, 689, 1947. (123) **Swineford, O., Jr.**: J. Allergy, **17**, 24, 1946.

(124) **Thieme, E. T.,** and **Sheldon, J. M.**: Ibid., **9**, 246, 1938. (125) **Tocker, A. M.,** and **Davidson, A. G.**: Ibid., **15**, 108, 1944. (126) **Turner, T. B.,** and **Hollander, D. H.**: Bull. Johns Hopkins Hosp., **87**, 505, 1950.

(127) **Vance, B. M.**, and **Strassmann, G.**: Arch. Path., **34**, 849, 1942. (128) **van Liere, E. J.**: Anoxia: Its Effect on the Body, Chicago, Univ. of Chicago Press, 1942. (129) **Vaughan, W. T.**, and **Derbes, V. J.**: J. Allergy, **12**, 477, 1941.

(130) **Waldbott, G. L., Kaufman, J. M.**, and **Merkle, K. J.**: Ibid., **21**, 339, 1950. (131) **Watson, S. H.**, and **Kibler, C. S.**: Ibid., **10**, 364, 1939. (132) **Weingarten, R. J.**: Lancet: **I**, 103, 1943. (133) **West, S.**: Brit. Med. J., **2**, 393, 1887. (134) **White, P. D.**: Heart Disease, ed. 3, New York, MacMillan, 1947. (135) **Wild, O.**, and **Loertscher, M.**: Schweiz. med. Wchnschr., **64**, 829, 1934. (136) **Willett, F. M.**, and **Oppenheim, E.**: Am. J. Med. Sci., **212**, 608, 1946. (137) **Wilson, J. L.**, and **Bradford, J. K.**: Structural Alterations of the Lungs. I. Cystic Disease; II. Emphysema; III. Pneumonoconiosis; IV. Atelectasis. Chapter in "Diseases" of the Chest", edited by Roscoe Pullen, Philadelphia, Lea & Febiger, (In press). (138) **Winer, B. M., Beakey, J. F.**, and **Segal, M. S.**: Ann. Int. Med., **33**, 134, 1950. (139) **Wise, H. S.**: New Orleans Med. & Surg. J. **101**, 576, 1949. (140) **Wiseman, J. R., Brown, B. T.**, and **Gandia, A. G.**: J. Allergy, **21**, 199, 1950. (141) **Wiseman, J. R.**, and **McCarthy-Brough, M. P.**: Ibid., **16**, 250, 1945. (142) **Wright, D. O.**, and **Gold, E. M.**: J. Am. Med. Assn., **128**, 1082, 1945.

(143) **Zahn, F. W.**: Virchow's Arch. f. Path. Anat., **123**, 197, 1891. (144) **Zuckermann, R., Calbrera, E. C., Fishleder, B. L.**, and **Sodi Pallares, D.**: Am. Heart J., **35**, 421, 1948. (145) **Zuelzer, W. W.**, and **Apt, L.**: Am. J. Dis. Child., **78**, 153, 1949.

PSYCHIATRY AND GERIATRICS: A REVIEW

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DURING the past decade the medical profession has shown a rapidly increasing interest in the aged segment of our population. Until recently the emphasis has been mainly on the organic aspects of the diseases of old age, with much less attention being paid to the psychological needs of older people. Even today many physicians, unfortunately, are convinced that all mental diseases of the elderly are "hopeless", and that custodial care in an institution is all that can be offered these unfortunate individuals.

It is the purpose of this article to review briefly some of the medical literature since 1949 that deals particularly with the psychiatric aspects of the diseases of the aged. Emphasis will be placed on those aspects of the subject which may be of interest to the general practitioner, who daily sees an increasing number of emotionally disturbed aged patients.

There is some confusion concerning the definition of terms which apply to this relatively new field of medicine. Dorland's dictionary defines *gerontology* as "the scientific study of old age, its phenomena, diseases, etc."; a *gerontologist* as "one specializing in the diseases of old age"; and *geriatrics* as "that department of medicine which treats of the diseases of old age." These terms obviously tend to overlap and are not specific. Stieglitz[20] simplifies the subject by defining *geriatrics* as "the care of the aged" and *gerontology* as "the study of the aging process." He points out that geriatrics should not be considered a specialty in the usual sense of the word, since it covers a wide field which intersects the various modern medical specialties. Geriatrics aims to prolong life and add value to it, so that old people may live their last years in reasonable comfort.*

Allen[1] states that geriatrics is an art, rather than a specialty, and it should not be considered solely that part of medical practice which treats organic illnesses of elderly patients. This author particularly stresses the need for geriatrics to direct its attention to the thoughts and feelings of the aged patient, in addition to treating his diseased organs.

It is common knowledge that the proportion of elderly people is rapidly increasing in the United States. Whereas the total population increased 73% between 1900 and 1940, the number of people over the age of 65 increased 190% during the same period[12]. In

* Ed. Note: *Gerontology* deals with all aspects of the problems of old age: medical, social, political, economic, and others. *Geriatrics* deals only with the *medical* aspects of gerontology.

1900, 1 in 25 living persons was over the age of 65; in 1950 this ratio had changed to 1 in 13[1]. This is naturally reflected in the number of aged people who develop mental diseases. Johnson[12] states that the number of patients over the age of 70 with involutional melancholia and senile psychoses admitted to mental hospitals between 1911 and 1936 increased about 180%. One can assume an even greater increase in the number of aged people suffering from less severe forms of emotional disturbance, who seek medical help from the general practitioner.

Tompkins[22], Ebaugh[7], Stieglitz[20], and others stress the importance of distinguishing between chronological and physiological old age. This is chiefly a socio-economic problem, since elderly people are refused employment or dismissed from active jobs solely on the basis of chronological age. Physicians have always been aware of the marked individual variations in physiological aging.

The general practitioner, despite his inevitable lack of specific psychiatric training, can do a great deal to help alleviate the emotional suffering of his aging patients. Many of these elderly people can be aided without calling for a psychiatric consultation or institutionalization.

The medical practitioner should naturally be able to recognize those severe mental disturbances which require psychiatric treatment. The "normal" mental changes of aging must be distinguished from pathological signs of emotional disorder. The physician can expect the patient over 65 to show a certain amount of increased self-centered preoccupation, irritability, garrulousness, forgetfulness, fear of approaching death, a gradual withdrawal from social activities, and a variety of other psychological changes.

Likewise, certain organic changes are considered to be "normal" in old age. Retinal arteriosclerosis of minimal degree is present in most elderly individuals. Gallinek[8] states that there is often little relationship between mental symptoms and the degree of brain damage due to cerebral arteriosclerosis or senile cortical atrophy. The mental syndromes "seem to be complex reaction types in which the anatomic factor is only one element in the constellation of causative agents." We do not know "why" a given patient develops a severe psychosis with associated cerebral arteriosclerosis, whereas another individual may live happily to a ripe old age, despite the fact that at autopsy there is apparent extensive cerebral vascular disease and senile degeneration. Nevertheless, it is true that the prognosis is much more favorable in those older patients who have "functional" mental disorders without evidence of associated somatic disease[4]. The physician must carefully evaluate the patient, both from the somatic and psychological viewpoints, before deciding to deal with the patient's emotional problems.

That the life-long personality configuration of an individual plays a major role in determining his attitudes toward growing old has been known since ancient times. Plato noted that "he who is of a calm and happy nature will hardly feel the pressure of age; but to him who is of an opposite disposition, youth and age are equally a burden." The physician can help the aging patient realistically to face the facts through the methods of persuasion, reassurance, and positive suggestion. People who have always had difficulty in adjusting to the demands of life may react to the inevitable loss of work, death of relatives and friends, loosening of family and social ties which acompany old age in our society

by developing psychiatric symptoms[9].

All types and degrees of mental disturbance are observed among elderly patients, ranging from mild transient psychoneurotic reactions to severe psychoses with organic brain disease. Granick[11] believes that emotional insecurity is the outstanding factor in the personality breakdown of the aged. This may include loss of economic security, inability to adapt to the loss of a marital partner, a failure to meet social obligations, loss of sexual desire, and others.

The need for the family physician to examine in some detail the psychological environment of the patient is emphasized by Ginzberg[10]. Frequently the aged patient hides his inner feelings from the physician. Well-meaning but excited relatives may give a distorted or veiled picture of the present illness and the patient's behavior at home. A thorough past history obtained from relatives sometimes can be of great value. Ginzberg[10] points out that it is not necessary for the doctor to delve deeply into his patient's inner conflicts. His main therapeutic goal is to help the patient to accept reality and, when feasible, to arrange a more suitable environment for him by suggesting new interests, changes in living arrangements, and the like. The old patient should be treated as a mature adult by the physician, who should counteract the common family attitudes regarding "second childhood." Sometimes the relatives wish to "get rid of" the patient, and in these instances the physician should support and reassure the patient, rather than accept the relatives' exaggeration of the degree of emotional disturbance he exhibits. Organic conditions should be carefully evaluated. It is easy for the physician to overlook organic disease in elderly neurotic patients and emotional disturbances in patients who have somatic disease[10]. Since more time is required in evaluating elderly patients than younger patients, the practitioner should not attempt to treat old people suffering from emotional disorders unless he is willing and interested enough to spend considerable time with his patient. The doctor who has limited time and who is primarily interested in the treatment of organic disease should refer old patients with emotional disorders to a physician whose particular talents or interests lie in the field of geriatrics.

Patience, understanding, and a genuine interest in the patient "as a person" are essential prerequisites for the physician who wishes to help this group of patients. Allen[1] believes the physician should make the patient feel he is personally interested in him and should try to share his interests. By a process of identification with the doctor, some elderly patients benefit markedly by this procedure.

Many elderly patients are mildly psychoneurotic and can be helped by the general practitioner. Unlike the psychotic, the neurotic recognizes that something is wrong but is unable to help himself. He may be anxious, have irrational fears, compulsions, or a wide variety of emotional symptoms which interfere with his inner sense of security and his capacity to adjust to other people in his environment or at work. The therapeutic goal is a gradual alteration in the patient's attitudes and way of life through positive suggestion, reassurance, and enabling the patient to ventilate his problems before a sympathetic counsellor in the person of the physician. The patient should be urged to develop personal independence throughout the treatment; and his sense of being useless, unwanted, and unimportant should be vigorously opposed[22].

Clow and Allen[6] studied a group of hospitalized psychoneurotic patients. Among 67 patients over the age of 60, 23 had never had a previous emotional illness. Minimal retinal arteriosclerosis was present in 37 patients. The commonest diagnosis was mixed psychoneurosis, showing a diffuse symptomatology. Somatic complaints were very common, despite the absence of organic disease.

The same authors state that the most common psychiatric disorders of the aged are depressive states and paranoid reactions[2]. In these conditions the patient's aggressiveness, formerly used in a healthy manner in the competition of everyday life, is either turned inward, in the depressed patient, or directed against neutral people in his environment, in the paranoid reactions. They found that 60% of 365 patients admitted to a private mental hospital showed a predominantly depressed mood[5]. An inverse relationship was noted between the degree of depression and the degree of organic mental deterioration. Patients who showed increasing mental changes due to organic brain disease tended to become less depressed and suicidal tendencies disappeared. Irritability was the most common symptom among the deteriorated patients.

The remainder of this paper will review recent literature concerning the diagnosis and treatment of major psychoses in elderly people. While the general practitioner cannot treat these patients, an awareness of the possibilities of helping these patients will help to dispel some of the misconceptions concerning the "incurability" of these conditions. If the physician notes severe agitation, suicidal ideas, paranoid delusions, hallucinations, or marked irritability and excitability, he should arrange for a psychiatric consultation or direct commitment to a mental hospital.

Modern methods of psychiatric treatment enable many hospitalized elderly patients to return to the community. About 38% of patients admitted to mental hospitals are classified as senile psychotics. This also includes patients with cerebral arteriosclerosis[22]. The distortions of thinking and behavior are based on individual personality characteristics which have been present throughout the patient's life and which appear in an exaggerated form during the psychosis.

Recent experience indicates that many psychoses of the aged are transitory, resulting from environmental or emotional upsets or toxic conditions. These individuals can recover just as readily as the younger group.

McGraw[15] cites the case of a 90-year-old man who developed a temporary psychosis following a head injury and who recovered completely after a short period of hospitalization. A woman of 70 developed a severe psychoneurosis due chiefly to enviromental stresses. After 2 years of hospital treatment, she returned to her own home and managed her own affairs[15]. In a study of 22 elderly patients hospitalized with toxic delirious reactions, Robinson[16] states that 21 recovered sufficiently to return home.

The psychiatrist can do very little for advanced cases of mental deterioration due to organic brain disease. These patients chiefly require custodial care in a mental hospital. Stieglitz[21] observes that when both physical and mental deterioration parallel each other, it is not as tragic as when the mind alone deteriorates and the patient lives on for many years as a mental invalid. However, many senile patients are relatively content as long as their physical needs are attended to.

Perhaps the most pathetic hospitalized group are the severely depressed aged patients. Many reports in the recent literature indicate dramatic improvement obtained through the use of electric shock therapy[3,4,6,11,13,15,16,18]. Kalinowsky and Hoch[13] found that patients with senile or presenile depressions beyond the involutional period responded equally well to electric shock therapy. The results depended upon how much organic brain damage was present. These authors state that organic brain disease is not a contraindication to the use of electric shock therapy. Bennett[3] found that sustained recoveries were quite common among patients over 80 who received electroshock.

In a study of 100 consecutive admissions of elderly patients to a private mental hospital, Chiles and King[4] found that 42% were suffering from primarily organic psychosis, 37% were primarily functional, and the remainder showed a mixture of organic and functional symptoms. Among 33 patients who were given electric shock therapy, 25 improved sufficiently to return home. This form of treatment is most successful in the affective disorders (reactive depression, manic-depressive psychosis, and involutional melancholia). Robinson[16] found that electric shock therapy benefits depressed or markedly excited patients over the age of 65, but recommends a conservative attitude in view of the risk of fractures of the long bones. This can be diminished by the use of curare prior to the treatment. The number of electric shock treatments given per week should be less than in younger patients, and treatment should be terminated as soon as possible[4].

Clow and Allen[8] "occasionally" gave electric shock therapy to psychoneurotic aged patients in the hospital, but found most of these patients did equally well without it. Sandritter[18] recommends electroshock in treatment of severe affective reactions, particularly if used in the early stages of agitation or depression.

The earlier contraindications to electric shock therapy in the elderly appear to be diminishing with further clinical experience. There is still general agreement that a recent coronary occlusion, cerebral vascular accident, or acute febrile disease are absolute contraindications to electric shock therapy. It must be emphasized, however, that electric shock therapy should only be administered by an experienced psychiatrist, preferably in a hospital. The decision to give electric shock treatment should not be placed on the cardiologist, geriatrician, internist, or general practitioner. This responsibility rests solely with the psychiatrist who, after careful medical consultation and evaluation, must weigh the risk involved against the intensity of the patient's mental suffering.

At present the overcrowded and inadequately staffed state mental hospitals provide very little therapy for the aged patient. Many authors[4,11,15,17,18,19,22] advocate an active treatment program which would include supportive psychotherapy, sedative tubs, occupational therapy, rehabilitation, active and interested nursing care, organized outdoor work and games, group pyschotherapy, and the like. Rusk[17] points out the need for developing a wide variety of social, medical, and psychiatric agencies in the community in order to prevent or diminish the present inadequate facilities for the care of aged patients. Stieglitz[20] feels that "preventive geriatrics" should devote itself to patients aged 40 to 60, and attempt to forestall future mental illness by helping them to face the realities of growing old.

The need for prolonged and adequate follow-up studies of elderly patients discharged from mental hospitals is discussed by Malamud and his coworkers[14]. These authors feel that no type of therapy is adequate unless it includes a long-range program of social readjustment of the patient. The psychiatrist and general practitioner should work together in helping these patients to adjust to their environment after leaving the hospital.

In conclusion, geriatrics represents an important and complex field of medicine, involving a combination of medical, socio-economic, and psychological factors. While the prognosis for elderly mental patients is certainly poorer than for the younger mentally ill, modern types of treatment are offering increasing hope to patients who formerly were considered beyond medical help. The physician's goal must be not only to prolong the physical existence of the aged patient, but to help him to live his last years in reasonable mental comfort.

REFERENCES

(1) **Allen, E. B.**: Geriatrics, **4**, 67, 1949. (2) Idem, and **Clow, H. E.**: Ibid., **5**, 66, 1950.
(3) **Bennett, A. E.**: Psychiatric Quart., **19**, 465, 1945.
(4) **Chiles, D. D.**, and **King, J. P.**: Virginia Med. Monthly, **77**, 531, 1950. (5) **Clow, H. E.**, and **Allen E. B.**: Geriatrics, **4**, 11, 1949. (6) Idem.: Ibid., **6**, 31, 1951.
(7) **Ebaugh, F. G.**: Private Communication, 1951.
(8) **Gallinek, A.**: J. Nerv. & Ment. Dis., **108**, 293, 1948. (9) **Gardner, W. P.**: Minnesota Med., **33**, 353, 1950. (10) **Ginzberg, R.**: Geriatrics, **5**, 35, 1950. (11) **Granick, S.**: J. Gerontology, **5**, 361, 1950.
(12) **Johnson, N. A.**: Mental Hygiene, **30**, 431, 1946.
(13) **Kalinowsky, L. B.**, and **Hoch, P. H.**: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune and Stratton, 1949.
(14) **Malamud, W., Sands, S., Malamud, I.**: and **Powers, P.**: Am. J. Psychiat., **105**, 567, 1949. (15) **McGraw, R. B.**: J. Gerontology, **4**, 234, 1950.
(16) **Robinson, G. W., Jr.**: in Mental Disorders in Later Life, O. J. Kaplan, Editor, Stanford, California, Stanford Univ. Press, 1945. (17) **Rusk, H. A.**: Am. J. Psychiat., **106**, 270, 1949.
(18) **Sandritter, G. L.**: Nebraska State Med. J., **34**, 384, 1949. (19) **Silver, A.**: Geriatrics, **5**, 146, 1950. (20) **Stieglitz, E. J.**: The Care of the Aging and Aged, 2nd ed., Philadelphia, W. B. Saunders, 1949. (21) Idem: The Second Forty Years, Phila., J. B. Lippincott, 1946.
(22) **Tompkins, H. J.**: Geriatrics, **6**, 57, 1951.

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PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MAY 15, 1951

The Effect of N-Allyl Normorphine in Treatment of Opiate Overdose. J. E. ECKENHOFF, M.D., J. D. ELDER, M.D., and B. D. KING, M.D. (Dept. Anesthesiol. and Harrison Dept. Surg. Res., Univ. of Penna.). N-allyl normorphine has been used in 23 patients who have been given large doses of morphine (up to 90 mg.), Demerol (up to 600 mg.) or who have had cyclopropane, ether, or pentothal as the primary anesthetic agents. Where respiration was depressed with either morphine or Demerol, 5 or 10 mg. of n-allyl normorphine intravenously resulted in a 2- or 3-fold increase in respiratory rate and a 200 to 300% increase in respiratory minute volume. The peak increase in minute volume was reached within 2 minutes, then declined, but remained well above the depressed level. Second doses were less effective and 3rd doses were ineffective. Pulse rate in the depressed individual declined after n-allyl normorphine. If the patient was hypotensive due to the narcosis, n-allyl normorphine uniformly caused a return toward the normal pressure, the peak rise accruing 5 to 10 minutes after injection. In normotensive patients there was no significant effect on blood pressure. A slight, but not remarkable, analeptic action was produced by the drug. N-allyl normorphine had no effect on depression produced by cyclopropane, pentothal, or ether.

N-allyl normorphine was administered intravenously (5 or 10 mg.) to 5 normal male volunteers. Respiratory rate was not remarkably affected. Respiratory minute volume was uniformly diminished (an average of 35%), the depression reaching maximum in 5 to 10 minutes and persisting for 40 or more minutes. Pulse rate and blood pressure were unchanged except in one individual whose pressure fell from 120/70 to 70/40. When tilted to 60°, 2 subjects fainted, 1 in 9 and the other in 10 minutes. All patients complained of a "tired feeling" and all developed a pallor similar to that observed when morphine is administered intravenously to normal subjects.

Quantitative Circulatory Response to an Acute Anoxemia Test in Dogs with Progressive Experimental Coronary Narrowing. E. L. FOLTZ, M. D., W. F. SHELDON, M.D., R. G. PAGE, M.D., J. J. SAYEN, M.D. and W. T. FITTS, M.D. (Depts. Med., Pharmacol., Pathol., and Surg. Res., Univ. of Penna.). Preliminary quantitative studies of the responses of coronary blood flow and cardiac O_2 metabolism to anoxemia have been obtained in intact anesthetized dogs with gradual coronary artery narrowing achieved by cuffs of cellophane and tantalum mesh. One or more studies were performed 21 to 166 days after placement of cuffs; 2 dogs had sham operations without cellophane cuff placement; normal dogs also were studied.

Under the resting circulatory state produced by the author's standard anesthesia (Dial, urethane, pentobarbital), there were no gross differences between dogs with coronary narrowing, sham operation dogs, and normal dogs in measurements of coronary flow, cardiac O_2 consumption, cardiac work, and cardiac rate. To date changes in response to anoxemia have been proportional to the degree of coronary narrowing.

Anoxemia levels from 55 to 70% arterial saturation were obtained with

inspired mixtures of low O_2 in N_2. Normal animals previously reported and sham operated dogs responded in approximately similar manner to the anoxemia. Dogs with slight coronary narrowing when subjected to anoxemia increased coronary flow over control levels slightly less (+78%) than did the normal dogs (+93%); cardiac O_2 consumption increased similarly (+50 to +55%) in both series. Increases in cardiac work and rate were slightly lower in dogs with narrowed arteries.

Dogs with moderate coronary narrowing showed considerably less augmentation of coronary flow (+55%) under anoxemia. Cardiac O_2 consumption failed to increase as greatly (+34%) as in normal dogs, but cardiac work and cardiac rate showed increases comparable to normal animals.

Two dogs with severe narrowing were tested. One died during the induction of anoxemia with ventricular fibrillation. The other dog sustained myocardial infarction during the anoxemia test, and final flow measurements were completed after electrocardiographic evidence of damage was recorded; in contradistinction to the rise in all other dogs, there was a fall in both coronary flow and blood pressure.

A Method of Collecting Bile in Rats; Normal Values on Rat Bile. BERNARD FISHER, M.D. and HARRY M. VARS, Ph.D. (Harrison Dept. of Surg. Research, Univ. of Penna.). The common bile duct of the 250-gm. male Wistar rat is cannulated with polyethylene tubing (PE 50) having an internal diameter of .023 inches. This is inserted into the proximal 1/3 of the duct, and is threaded to the bifurcation of the hepatic ducts where it is anchored by fine silk ligatures. Such a position is essential so as to avoid the collection of pancreatic juice which empties into the lower 2/3 of the common duct through multiple pancreatic ducts. The tube is brought out of the body through the right flank and is tunneled under the skin of the posterior body wall to emerge in the midline of the back. Bile is collected in a latex bag placed in a plastic cylinder anchored to the back by adhesive tape. This permits practically unconfined movement in a regular cage. Bags are changed every 24 hours. One per cent saline solution as drinking water is given all rats. To date this procedure has been employed upon 65 rats. Bile collections have been made in rats for a 54-day period, they then being sacrificed in good health. Volume, total solids, nitrogen content, total cholic acids, and total cholesterol secretion have been studied in rats fed an 18% protein diet and a nonprotein diet for a 14-day period.

When receiving protein (14 rats), the average daily volume of bile was decreased following operation but reached a level on the 5th day which was maintained for the next 9 days at 10 to 12 ml./24 hours. Total bile acid secretion was suppressed following operation to about half that observed on the 4th to 14th days, that is, 35 to 40 mg./24 hr. Total cholesterol ranged from 0.8 to 2.0 mg./day.

In protein-depleted animals (7) bile volume averaged 6 to 8 ml./day and the total cholic acid secretion gradually decreased from 20 mg. to 12.0 mg./24 hr. over the 2-week period. Total cholesterol was 0.5 to 1.5/24 hr.

(This work was performed under a contract between the Department of the Army and the University of Pennsylvania).

An Analysis of Some Responding and Spontaneous Forms Found in the Electrical Activity of the Cortex[*]. JOHN C. LILLY, M.D., and RUTH CHERRY

[*] This investigation is supported in part by a grant from the Division of Research Grants and Fellowships of the National Institutes of Health, U. S. Public Health Service.

(E. R. Johnson Foundation, University of Penna.). By the use of a technique which records from 25 electrodes simultaneously†, spatial forms have been discovered in the electrical activity of the cortex of cats' brains. Both the responses to end-organ stimuli and the so-called spontaneous activity are seen to have a spatial organization which changes with time and with place on the cortex. Characteristically, a response is seen as a wave spreading radially from an initial locus, traveling to the edge of the projection area, and spilling over into an adjacent area. This responding form is very sensitive to barbiturate anesthetics. Deepening anesthesia slows the wave in both the projection area and the adjacent region and shortens the distance traveled into the latter. The velocity of the wave in the projection area is about 10 times that in the adjacent area.

Spontaneous forms are less stereotyped than the responding ones. They have a multiplicity of shapes, of directions of travel, of origins, and of terminations. These forms are also sensitive to anesthetic: at a light level they are small, rapid, and about equally frequent in all regions; at deeper levels they become larger, slower, less frequent, and more unique in each region. By averaging the behavior of one type of these forms, characteristic of one region, trends have been found in their behavior.

Analyses of the time, course of responding, and spontaneous forms have been made and will be presented. The projection area analyzed is the acoustic one; the adjacent region analyzed is the "association" area in the posterior ectosylvian gyrus. The spontaneous forms analyzed occur only in the "association" area.

A Technic for Preserving Structure in Specimens for Electron Microscope Studies: Stereoscopic Electron Microscopy.* THOMAS F. ANDERSON, Ph.D. (Johnson Foundation and Dept. of Med. Physics, Univ. of Penna.). Before specimens can be examined in the high vacuum of the electron microscope they must be dried. This drying normally involves the passage of an air-water interface through the specimen and this deforms all but the most rugged structures. These structural changes can be minimized by eliminating the force of surface tension in the drying process. This is done by substituting for the water in the specimen a series of *miscible* liquids in turn, the last of which is a liquid like carbon dioxide under pressure of 25° C. Then when the temperature is raised above the critical point of the final liquid (31° C. for carbon dioxide), the liquid is made to change imperceptibly into a gas. Upon the release of this gas, the specimen will have been dried without having suffered the damaging passage of a phase boundary through it‡. The structures of hemolyzed erythrocytes, bacteria, bacteriophages, etc., are largely preserved after they have been dried in this way and can be viewed to advantage in stereoscopic electron micrographs.

† Lilly, J. C.: A Method of Recording the Moving Electrical Potential Gradients in the Brain: the 25-Channel Bavatron and Electro-icono-grams, AIEE-IRE Conference on Electronics in Nucleonics and Medicine (S-33), New York. Amer. Inst. of Electr. Engineers, 1950, pp. 37-43.

* This work was supported by a contract between the Office of Naval Research, Department of the Navy and the University of Pennsylvania (NR-135-197), Physical, Chemical, and Biophysical Characterization of Viruses and Virus Systems. Reproduction of this article in whole or in part is permitted for any purpose of the U. S. Government.

‡ Anderson, T. F., Trans. New York Acad. Sci. 13, 130-134, 1951.

BOOK REVIEWS AND NOTICES

GENETIC NEUROLOGY. Edited by P. WEISS, Univ. of Chicago. Pp. 239; ills. Chicago: Univ. of Chicago Press, 1950. Price, $5.00.

THIS volume of Genetic Neurology contains the papers given on a symposium under the chairmanship of Dr. Carl Wyss of the University of Chicago, as a part of the International Health Organization Program. The field designated by this name includes studies of growth and development of the nervous system and repair after injury.

This book is a valuable summary of contemporary thought by distinguished investigators in this field. The term "Genetic Neurology" seems inapt to this Reviewer because it suggests a narrower vista than is actually included. Some of the work on the regeneration of human nerve is of immediate practical interest. G. G.

COMMUNITY HEALTH EDUCATOR'S COMPENDIUM OF KNOWLEDGE. By CLAIR E. TURNER, A.M., Ed.M., D.Sc., Dr. P.H., Prof. of Public Health Emeritus, Mass. Inst. of Technol. Pp. 266; ills. St. Louis: C. V. Mosby, 1951. Price, $3.00.

THIS is an excellent handbook for physicians, health educators, public health nurses, workers in voluntary health agencies, and others on the principles, possibilities, and procedures in democratic activities for the promotion of health. Well planned and concisely written, and containing numerous illustrations, it gives useful information on how to work with others effectively, get results from committee meetings, and make adequate preparations for public meetings, and how to prepare good publicity, printed matter, and exhibits. J. K.

THE 1950 YEARBOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY. Edited by ROLAND P. MACKAY, M.D., Prof. of Neurology, Univ. of Ill.; NOLAN D. C. LEWIS, M.D., Prof. of Psychiatry, Columbia Univ.; and PERCIVAL BAILEY, M.D., Prof. of Neurology and Neurosurgery, Univ. of Ill. Chicago: Yearbook Publishers, Inc., 1951. Price, $5.00.

THIS book maintains its previous high caliber. The sections devoted to neurology, psychiatry, and neurosurgery are well balanced and contain carefully edited abstracts of articles important to all practitioners regardless of specialty. Each section is preceded by a summary which outlines the progress made in that field during the decade 1940 to 1950. The comments of the editors are interesting and instructive. M. S.

TOXICOLOGY OF URANIUM. Edited by ALBERT TANNENBAUM, M.D., Director, Dept. of Cancer Res., Medical Res. Inst., Michael Reese Hospital, Chicago, and by 14 contributing authors. Pp. 333; 44 charts and diagrams, 24 ills. Volume 23 of Division IV of the National Nuclear Energy Series. New York: McGraw-Hill; 1951. Price, $3.00.

THIS book is a good example of lithoprinting though the reproduction of photographs is not as good as one would like. The first 50 pages, Part A, "Introduction to the Toxicology of Uranium," presents a brief survey of the significant findings" while the remainder of the book presents the complete original studies made by a number of workers for the Manhattan Project by the Metallurgical Laboratory of the University of Chicago and, through subcontract, by the Medical Research Institute of Michael Reese hospital. The volume is not intended as a complete textbook of uranium pharmacology and toxicology, but gives references to other literature, including a 12-page "Introduction to the Nonclassified Literature Dealing with Biochemical Studies of Experimental Uranium Poisoning." The book is not primarily of interest to the average physician, but is of interest to those dealing with health aspects of atomic energy projects, to toxicologists, and to biochemists. R. H.

THE NEUROSES. By WALTER C. ALVAREZ, M.D., Prof. of Medicine Emeritus, Mayo Foundation, Univ. of Minnesota. Pp. 667. Philadelphia: W. B. Saunders, 1951. Price, $10.00.

ONE is pleased to review a book written by the keen clinician who has now seen 140,000 sick persons and feels that the "ideal book in neuroses for a non-psychiatrist would have to be written by a fellow non-psychiatrist." The astute observations of the master internist are in evidence throughout the book.

But when he steps out of the field of descriptive psychiatry in its superficial aspects

and states that the trouble with psychiatry today is that so little is known about etiology (p. 24) he shows an obvious lack of knowledge of the fast-growing field of dynamic psychiatry. This is probably one of the largest books (667 pages) devoted just to the neuroses and yet there is only 1 mention of Freud (p. 614), and not 1 listing in the bibliography, a characteristic deficiency in this book, while it pauses to praise "Anomaly" by an anonymous author who wrote a book on the "Invert and His Social Adjustment."

The importance of heredity is overemphasized and again many authorities are quoted, but not Kallman, who is recognized as the present day leader in the field.

There are excellent chapters of such topics as "On Determining the Causes of Pain" and "Ordering or Not Ordering Tests," which are incidentally couched in such picturesque language as "the best proofs . . . of how completely decerebrate the 'thorough' practice of internal medicine can become . . ."

The treatment of the psychoneuroses, for example, hysteria, is completely inadequate from today's standards. His approach to the treatment of the neuroses is formulated under "Help a Non-psychiatrist Can Give a Nervous Patient." It is superficial, educational, and inspirational in type. The physician, particularly, the author implies, would seem to need this inspirational type of therapy and the bibliography is very catholic.

This is not a book to be used as a graduate course for the young physician (as the author recommends in the preface). He has learned to subsist on the staples of dynamic psychiatry. Rather this volume should be sipped as a vintage of rare but ancient brew in these days of potential "state store" distribution of medical education. H.F.

NUTRITION AND CHEMICAL GROWTH IN CHILDHOOD, Vol. 3, Calculated Data. By ICIE G. MACY, Ph.D., Sc.D., Director of the Research Laboratory, Children's Fund of Michigan. Pp. 1461-2174. Springfield, Ill.: Charles C Thomas, 1951. Price, $8.00.

THE 3rd volume of this series is a natural sequel to the first 2 volumes, which present the methods employed and the physical and chemical data on the children utilized for the extensive and meticulous studies carried out by Macy and her group. In this latest addition to the series, the average daily values for intakes, absorption, and retention of nitrogen, carbohydrate, fat, and various minerals are recorded not only for the individual children, but, what is more important, they are grouped and recorded according to age, body weight, body length, body surface and intakes of the respective food substances. The index is inclusive for the 3 volumes. For the investigator, this last volume will be of inestimable value. W.N.

AMINO ACIDS AND PROTEINS. Theory, Methods, Application. Compiled and edited by DAVID M. GREENBERG, Ph.D., Prof. of Biochem., Univ. of Calif., Berkeley. Pp. 950. Springfield, Ill.: 1951. Price, $15.00.

SOME 18 contributors, specialists in their own particular fields, have joined to make this the most modern textbook covering this subject. In the 13 chapters, the chemical, physical, and biologic characteristics of amino acids and proteins are presented concisely, together with adequate tables of information and bibliographic references. The major topics covered include chemical characteristics of amino acids and methods of isolation, purification, and determination; and classification, isolation, molecular size, amphoteric properties, reactions, and criteria of purity of proteins. Of particular interest are the discussions of the chemistry of antibodies, biological properties of plasma proteins and protein hormones, and the metabolism and nutritional applications of amino acids and proteins. H. V.

NEW EDITIONS

The Students' Handbook of Surgical Operations. By FREDERICK TREVES. Revised by CECIL WAKELEY, Senior Surgeon to Kings College Hospital. 9th ed. Pp. 580; 269 ills. New York: Paul B. Hoeber, Inc., 1951. Price, $5.50.

THIS handbook describes the technique of practically all the operations of general surgery. One criticism might be that less space should be devoted to position of patient, placement of incision, and specific instruments used. The space thus saved could be applied to the more important aspects. For example, in the section on thyroid surgery, the position of the recurrent laryngeal nerves is not mentioned and their injury is not included among the postoperative complications. Also, the treatment of varicose veins is described in 2 pages and only sclerosing therapy is given.

There are various points which differ from the general teaching in this country. For instance, catgut and kangaroo tendons are their sutures of choice.

This handbook could be recommended to the general surgeon or post-graduate student, but its value to medical students is open to question.

R. B.

Synopsis of Surgical Anatomy. By ALEXANDER LEE MCGREGOR, Senior Surgeon of Johannesburg General Hosp. 7th ed. Pp. 778;

746 ills. Baltimore: Williams and Wilkins, 1950. Price, $6.50.

The author uses diagrammatic sketches effectively to illustrate certain significant factors in surgical anatomy. It seems that little, if anything, which might be of value to the surgeon has been omitted.

The section on anatomy of congenital abnormalities contains the essentials of embryology as well as the abnormal anatomy and makes the entire subject more understandable. This book is obviously not meant to replace or compete with standard anatomic textbooks, but it should be of great value to the surgeon or student of surgery as a review and reference volume. R. B.

Nasal Sinuses. By O. E. VAN ALYEA, M.D., Assoc. Clin. Prof., Dept. of Laryng., Rhin. and Otol., Univ. of Ill. Coll. of Med. 2nd ed. Pp. 327; 142 ills. Baltimore: Williams & Wilkins, 1951. Price, $9.00.

THE factual information of this book is extremely well supplemented by excellent illustrations. The histology, pathology, embryology, and clinical material are excellently organized and correlated. The physiology is not quite complete. For example, the author omitted the relationship of the upper and lower cartilages, the nasal vestibule, and the columella to the air currents and their effect on the positive and negative air pressures which ultimately affect the sinuses.

In the chapter, "Diagnosis of Sinusitis," the nasopharyngoscope is only casually mentioned and the reader is led to assume that it is unimportant. This instrument is practically indispensable, especially in the diagnosis of a tumor in the epipharyngeal region. Without its aid many a diagnosis would fail.

The use of lipiodol has been overemphasized; actually, it is not always feasible to inject it for diagnostic purposes. Sufficient information on the technique of block anesthesia is lacking, and preparation for major surgery should have been stressed, such as sedation and the giving of Vitamins K and C. These measures prevent or minimize ecchymosis and swelling postoperatively.

The author should be congratulated for debunking the use of various nasal tamponages and nasal medication. One does not encounter many cases of argyrosis since the silver preparations are no longer commonly employed. The words "radical surgery" have been used much too freely; their overuse has almost caused them to lose their true meaning. Substitution from time to time of the term "major surgery" would have indicated use of surgical judgment by the rhinologist.

The anatomy of the frontal sinus and the irregularity of the nasal frontal duct is well described. The section on the differential diagnostic point for probing the frontal sinus is most appropriate. The author has failed, however, to stress the dangers of Roentgen-ray therapy in allergic and hyperplastic sinusitis. He has neglected to mention the fact that the edema induced by this therapy may result in closure of the sinus ostia and in complete obstruction of drainage.

The chapter on sinusitis in children is a classic. A timely warning has been given concerning the removal of tonsils and adenoids. The management of polypi was approached much too conservatively. A chapter on ozena and atrophic rhinitis might have been included as well as vaccine therapy and the preparation of a filtrate from the nasal secretions.

Finally, the price of this 2nd edition is much too costly. Use of many of the previous illustrations (anatomy does not change between 1st and 2nd editions) might have cut down the price. M. E.

Principles and Practice of Bacteriology, College Outline Series. By ARTHUR H. BRYAN, Univ. of Baltimore and Union Mem. Hosp., and CHARLES G. BRYAN, Port and Llympia Hosp., England. 4th ed. Pp. 410; 79 ills., 2 color plates. New York: Barnes and Noble, 1951. Price, $1.75.

THIS booklet belongs to the well-known College Outline Series which for many years has been used widely by students in cramming for examinations. It is obviously intended for the sophomore medical student preparing for Part I of the National Boards, since the questions from 1947 through 1949 are appended. Few of the answers to these questions are within the covers. The book can be used as a study guide because of its excellent index, glossary, and references. About ½ is devoted to medical bacteriology. The terminology is modern but the text is not up to date. This is neither an authoritative guide for the beginning medical student nor an adequate source of information for the graduate physician. E. S.

Clinical Parasitology. By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), Sc.D. (Hon.), F.A.C.S., F.A.C.P., D.S.M., late Colonel, U. S. Army, formerly Director, Army Med. Sch., and Assist. Commandant, Army Med. Center, Washington, D.C.; Emeritus Prof. of Trop. Med., Tulane Univ. of La.; and ERNEST CARROLL FAUST, M.A., Ph.D., William Vincent Prof. of Trop. Dis. and Hyg. and Head, Div. of Parasitol., Dep. of Trop. Med. and Publ. Health, Tulane Univ. of La.; consultant to the Surgeon General, U. S. Army; consultant U. S. Public Health Serv. 5th ed. Pp. 976; with 326 ills., 6 colored plates. Philadelphia: Lea & Febiger, 1951. Price, $12.00.

THE 5th edition of this classic has been completely revised and expanded to keep abreast of the newer developments in the science. The text has been completely reset and, in contrast to previous editions, the less important textual material is set in smaller type.

There are no fundamental changes in the general presentation of the subject but there are many additions. Therapy includes a discussion of the more recent chemotherapeutic agents and the antibiotics. Several new, well-chosen and excellently reproduced illustrations (some in color) have been added.

A notable feature is the new chapter, by Albert Miller, on the control of medically important arthropods. The sections on parasitologic techniques and references to the literature are brought up-to-date.

The book will continue to be a standard text for both students and physicians. A. L.